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Chemo-, Diastero-, and Regioselective C–c and C–o Bond formation via Transition Metal Catalysis

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Abstract
The efficient stereoselective formation of C–C and C–O bonds remains a critical challenge in organic chemistry. The level difficulty of these bond formations increases dramatically when regio-, diastereo-, and chemoselectivity issues are present. In efforts to address such challenges, this thesis summarizes three successful strategies to develop highly stereoselective C–C and C–O bond formation reactions: 1) the first strategy outlines the direct metallation and subsequent chemo- and regioselective cross-coupling of benzylic sp3-hybridized C̄H bonds (pKa values >34) to form C–[illegible] bonds via palladium catalyzed deprotonative cross-coupling process (DCCP), 2) the second strategy outlines the application of 1,1-heterobimetallic borozinc reagents in the diastereoselective C–[illegible] bond-forming reactions, and 3) the third strategy outlines the use of transition metal-catalysis in the highly chemo- and diastereoselective C–O bond formation via vanadium catalyzed directed epoxidation.

Chapters 1 and 2 summarize a program that we have recently initiated in our laboratory known as deprotonative cross-coupling process (DCCP). DCCP is the reversible in situ deprotonation of weakly acidic sp3-hybridized C-H bonds under mild conditions, which are then catalytically cross-coupled with aryl electrophiles under palladium catalysis.

Chapters 3 and 4 summarize the potential usefulness of 1-alkenyl-l,l-heterobimetallics in the stereoselective C–C bond formations in organic synthesis. Our group reported a practical generation of 1,1-heterobimetallics from air-stable B(pin)-substituted alkynylboronate esters and demonstrated their utility in a variety of one-pot transformations to provide boron-substituted allylic alcohols, dienols, α-hydroxy ketones, and α-dihydroxy ketones with high diastereoselectivity. More applications of these reagents are also explored in Chapters 3 and 4.

In Chapter 1 (Scheme 1), we have developed the first metal-catalyzed direct α-arylation of unactivated allylbenzenes (pKa ~ 34 in DMSO) with aryl bromides to afford 1,1-diarylprop-2-enes via a deprotonative cross-coupling process.

Usually the combination of aryl bromides, allylbenzene, base and a palladium catalyst results in a Heck coupling reaction. Herein we combine these same reagents, but override the Heck reaction through use of a strong base. While the base controls the chemoselectivity, the catalyst handles the regiochemistry, affording 1,1-diarylprop-2-ene products that are inaccessible via the Heck pathway (Scheme 1). The significance of this work is that it demonstrates that very weakly acidic hydrocarbon frameworks can be functionalized under DCCP conditions. The palladium-catalyzed arylation proceeded efficiently in the presence of PCy3 and produces α-arylated 1,1-diarylprop-2-enes in good to excellent yields (51-97%) with very high regioselectivity (>95:5).

Scheme 1: Overriding Heck Cross-Coupling Selectivity: Chemo- and Regioselective C(sp3)–H Activation in the α-Arylation of Unactivated Allyarenes via a Palladium-Catalyzed Deprotonative Cross-coupling Process.

Chapter 2 introduces the synthesis of diarylmethylamines via functionalization of weakly acidic sp3-hybridized C-H bonds adjacent to nitrogen in benzylic amines.

Direct deprotonation of the benzylic C–H's in secondary benzylamine derivatives under catalytic conditions is very challenging. This result is due to the weak acidity of sp3-hybridized benzylic C-H bonds adjacent to nitrogen, which requires strong organometallic bases such as alkyl lithiums for deprotonation. These strong bases, however, are impractical for cross-coupling reactions due to their limited compatibility with catalysts and coupling partners. We, therefore, envisioned the reversible in situ metallation/deprotonation and subsequent palladium catalyzed cross-coupling of the N-Boc benzylalkylamines with aryl electrophiles to form C–C bonds via deprotonative cross-coupling processes (DCCPs).

In Chapter 2 (Scheme 2), we, therefore, disclose the first direct cross-coupling of N-Boc benzylalkylamines with aryl electrophiles to provide N-Boc diarylmethylamines in moderate to high yields (50̃93%, 29 examples). Upon removal of Boc group, secondary diarylmethylamines are generated (75̃95% yields, 2 examples).

Scheme 2: Palladium Catalyzed DCCP of N-Boc Benzylmethylamine derivatives followed by Deprotection to generate Diarylmethylamines.

In Chapter 3 (Scheme 3), we disclose the vinylation of N-(2-pyridylsulfonyl) aldimines with versatile alkenyl-1,1-borozinc heterobimetallic reagents to furnish B(pin)-substituted allylic amines with high stereoselectivity in 60-93% yield in a one-pot procedure. The addition step can be followed by either [illegible]C bond oxidation to provide α-amino ketones (71-98% yields) or Suzuki cross-coupling to provide densely functionalized trisubstituted (E)-allylic amines (51-73% yields).

Scheme 3: Addition of Alkenyl-1,1-heterobimetallics to N-Pyridyl Sulfonyl Imines: Stereoselective Synthesis of B(pin)-substituted Allylic Amines, α-Amino Ketones, and Trisubstituted (E)-Allylic Amines.

As part of our program in developing stereoselective C-C bond forming reactions, we have reported the generation of 1-alkenyl-1,1-heterobimetallic reagents based on boron and zinc from readily available, air-stable B(pin)-substituted alkynes. Thus, regioselective hydroboration of B(pin)-alkynes generates the 1,1-bis (boro) intermediates. Chemoselective transmetallation of the more reactive vinyl-BCy2 bond generates 1-alkenyl-1,1-heterobimetallic reagents. The difference in reactivity between Zn-C vs. B̃C bonds allows for selective reaction at the Zn-C bond with aldehydes to yield B(pin)-substituted allylic zinc alkoxide intermediates. The alkoxide intermediates were then employed in various tandem reactions to form an array of compounds such as B(pin)-substituted allylic amines, α-amino ketones and trisubstituted (E)-allylic amines.

In Chapter 4 (Scheme 4), a retrosynthetic disconnection for the stereoselective preparation of α,α′-dioxygenated carbonyl compounds is disclosed. Herein we report a method to divert the oxidation of vinyl boronate esters from the B-C bond to the C=C bond, resulting in a new stereoselective class of oxidation products from vinyl boronate esters. Treatment of 2-B(pin)-substituted allylic alcohols with catalytic OV(acac)2 and TBHP resulted in a highly chemo- and diastereoselective directed epoxidation to provide B(pin)-substituted epoxy alcohols (55-96% yield, dr > 20:1). In the case of B(pin)-substituted bis-allylic alcohols, highly substituted bis-epoxy alcohols with five contiguous stereocenters were obtained (dr >20:1). Furthermore, the difference in reactivity between allylic alcohols and 2-B(pin)-substituted allylic alcohols towards epoxidation enabled the selective oxidation of the allylic alcohol in the presence of TBHP and VO(acac)2. The reactivity difference between the two allylic alcohols suggests C=CB(pin) to be more electron deficient than C=C(alkyl). The B(pin)-substituted epoxy alcohols are also useful synthetic intermediates. Tandem vanadium catalyzed epoxidation of the 2-B(pin)-substituted allylic and bis-allylic alcohols with excess TBHP generated the intermediate epoxides and bis-epoxides, respectively. Subsequent addition of NaOH resulted in the oxidation of the B-C bond of the B(pin)-substituted epoxides to afford

2-keto-anti-1,3-diols (30-83% yield) and epoxide-substituted 2-keto-anti-1,3-diols (61-78% yield, dr >20:1). The latter underwent a novel facile acid-mediated cyclization to furnish fully substituted dihydroxy-tetrahydrofuran-3-ones (65-92% yield, dr >20:1). Such compounds are difficult to efficiently access via conventional synthetic methods.

Scheme 4: Diastereo- and Chemoselective Dual Oxidation of B(pin)-substituted Allylic Alcohols: Synthesis of Epoxy Alcohols, 2-Keto-anti-1,3-diols and Dihydroxy-tetrafuran-3-ones.

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CHEMO-, REGIO-, AND DIASTEREOSELECTIVE C–C AND C–O BOND FORMATION VIA TRANSITION METAL CATALYSIS

Nusrah Hussain

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Supervisor of Dissertation:

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CHEMO-, REGIO-, AND DIASTEREOSELECTIVE C–C AND C–O BOND FORMATION VIA TRANSITION METAL CATALYSIS

Dedicated to

My parents: Dr. Musharraf Hussain and Mrs. Mahmuda Musharraf

My husband: Dr. Abdullah Al-Nayeem

My siblings: Dr. Deena A. Hussain, Dr. Mahmud M. Hussain and Dr. Bushra Hussain

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Last but not the least, all praise belongs to **Allah**, the Almighty God, who helped me in completing my doctoral thesis. It would have not been possible without His

continuous blessings, help and support. I am happy to glorify His name in the sincerest way through this small accomplishment.

ABSTRACT

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Nusrah Hussain

Patrick J. Walsh, Ph.D.

The efficient stereoselective formation of C–C and C–O bonds remains a critical challenge in organic chemistry. The level difficulty of these bond formations increases dramatically when regio-, diastereo-, and chemoselectivity issues are present. In efforts to address such challenges, this thesis summarizes three successful strategies to develop highly stereoselective C–C and C–O bond formation reactions: 1) the first strategy outlines the direct metallation and subsequent chemo- and regioselective cross-coupling of benzylic sp^3-hybridized C-H bonds (*p*Ka values >34) to form C–C bonds via palladium catalyzed deprotonative cross-coupling process (DCCP), 2) the second strategy outlines the application of 1,1-heterobimetallic borozinc reagents in the diastereoselective C–C bond-forming reactions, and 3) the third strategy outlines the use of transition metal-catalysis in the highly chemo- and diastereoselective C–O bond formation via vanadium catalyzed directed epoxidation.

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In Chapter **1** (Scheme 1), we have developed the first metal-catalyzed direct α-arylation of unactivated allylbenzenes (pK_a ~ 34 in DMSO) with aryl bromides to afford 1,1-diarylprop-2-enes via a deprotonative cross-coupling process.

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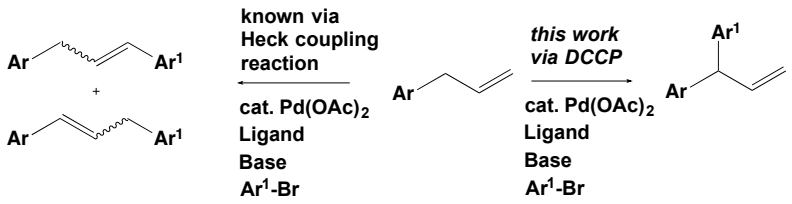

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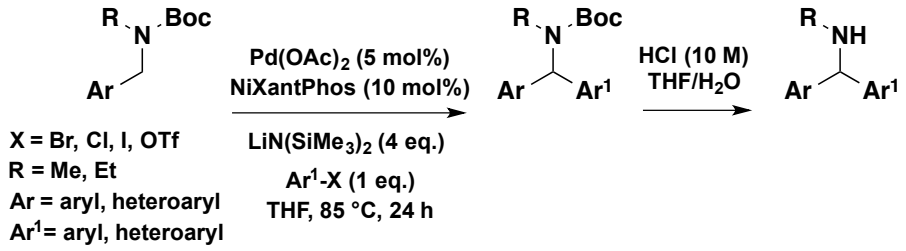

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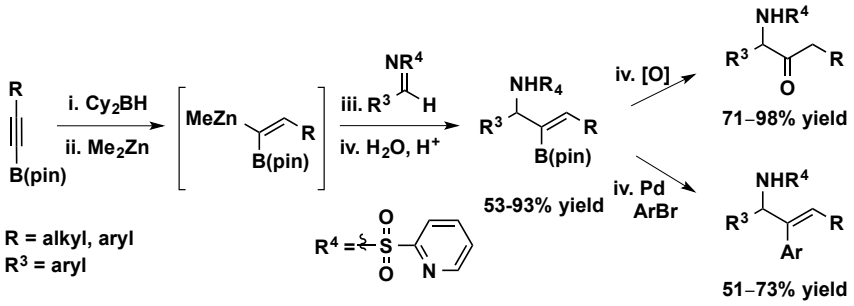

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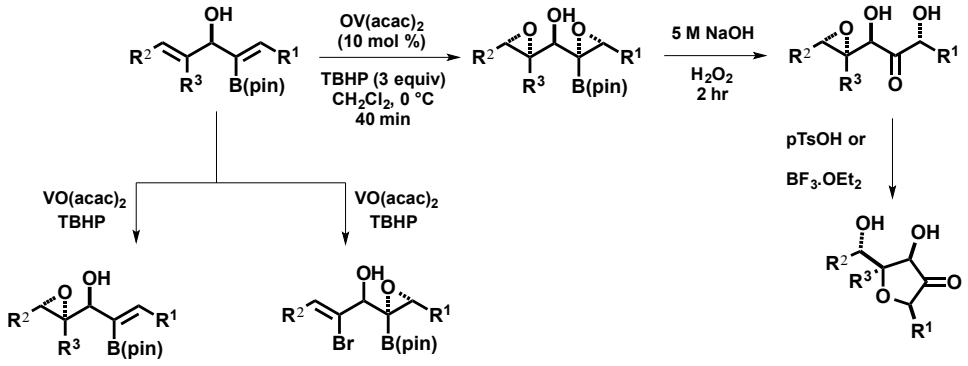

Scheme 4: Diastereo- and Chemoselective Dual Oxidation of B(pin)-substituted Allylic Alcohols: Synthesis of Epoxy Alcohols, 2-Keto-anti-1,3-diols and Dihydroxy-tetrafuran-3-ones.

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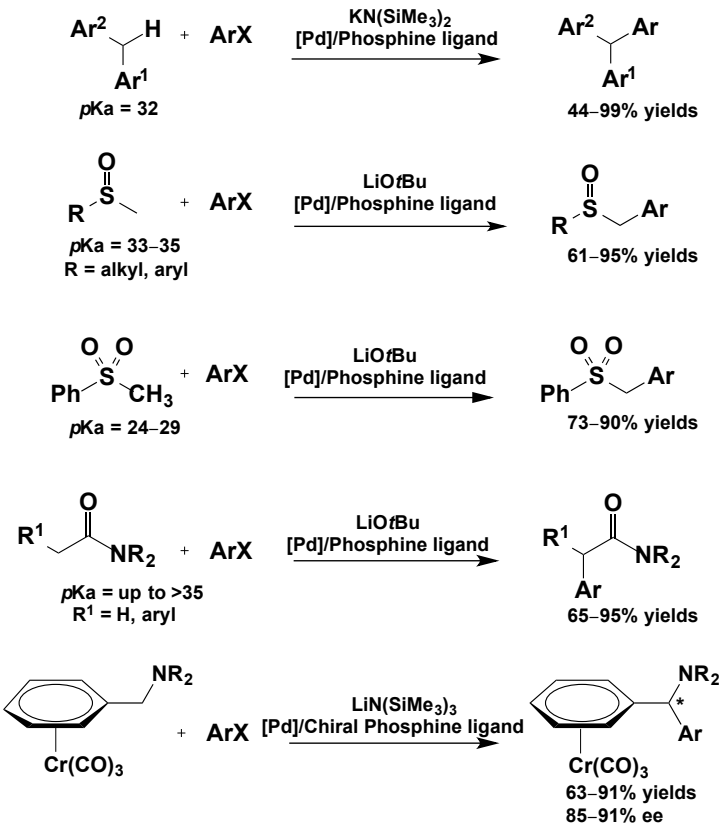
CHAPTER 1
Chemo-, and Regioselective sp^3 (C–H) Arylation of Allylarenes via Palladium Catalyzed Deprotonective Cross-Coupling Processes[i]

1. Introduction:

Catalytic functionalization of weakly acidic sp^3-hybridized C–H bonds in the absence of directing groups is highly desirable, but remains challenging.[1][2] The level of difficulty of these functionalizations increases dramatically when regio- and chemoselectivity issues are present. In our efforts to address such challenges, we recently initiated a program for the functionalization of weakly acidic sp^3-hybridized C–H bonds by palladium catalyzed deprotonative cross-coupling processes (DCCP). Substrates that have been successfully functionalized using this approach include diarylmethanes,[3, 4] sulfoxides,[5] sulfones,[6] amides,[7] and chromium-activated benzylic amines (to produce enantioenriched diarylmethylamines) (Scheme 1).[8]

Based on these results, we hypothesized that it might be possible to functionalize allylbenzene derivatives and control chemo- and regioselectivity. Successful development of such a process would require: 1) conditions for the deprotonation of allylbenzene that are amenable to catalysis, 2) catalysts that can promote the regioselective arylation, and 3) control of base reactivity such that the more acidic product is not deprotonated and isomerized or further functionalized.

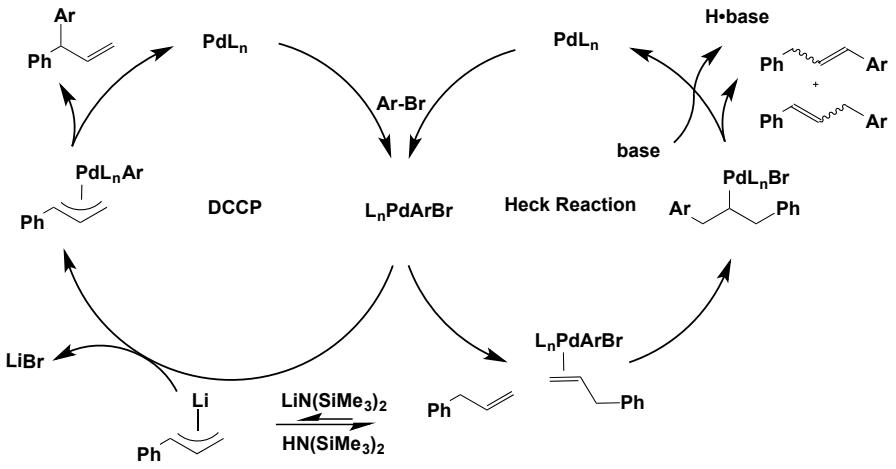
[i] [N. Hussain, G. Frensch, J. Zhang, P. J. Walsh, "*Chemo- and Regioselective C(sp^3)–H Arylation of Unactivated Allylarenes by Deprotonative Cross-Coupling*," Angew. Chem., Int. Ed. **2014**, *53*, 3693-3697] – Reproduced by permission of The © 2014 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.



Scheme 1: DCCP of Diarylmethanes, Sulfoxides, Amides, and Chromium-activated Benzylic Amines.

Typically, reactions of allylbenzenes with aryl bromides in the presence of palladium catalysts and base afford Heck–type γ-selective products, often as mixtures of regio- and geometric isomers (Scheme 2, right).[9][10] We envisioned that a strong base could divert the chemoselectivity from olefin coordination and insertion of allylbenzene in the Heck coupling to transmetallation of the metallated allyl (Scheme 2, left).[11, 12] The catalyst/ligand combination would control the regioselectivity of the arylation in the DCCP, thus enabling the formation of α-arylated products that are inaccessible via the Heck pathway. It is noteworthy that this approach is distinct from known C–H activation/arylations of allylbenzenes and related substrates.[13]

Herein, we disclose the first metal-catalyzed C(sp^3)–H arylation of allylbenzenes (pK_a ~ 34 in DMSO)[14] with aryl bromides to afford 1,1-diarylprop-2-enes. A base/catalyst combination [$LiN(SiMe_3)_2$/Pd-PCy_3] is advanced that efficiently controls the chemoselectivity and promotes regioselective DCCP of allylbenzenes in good to excellent yields (51–97%).



Scheme 2: Overriding Heck Coupling: Heck Reaction (right) vs. DCCP of Allylbenzene with strong Base (left).

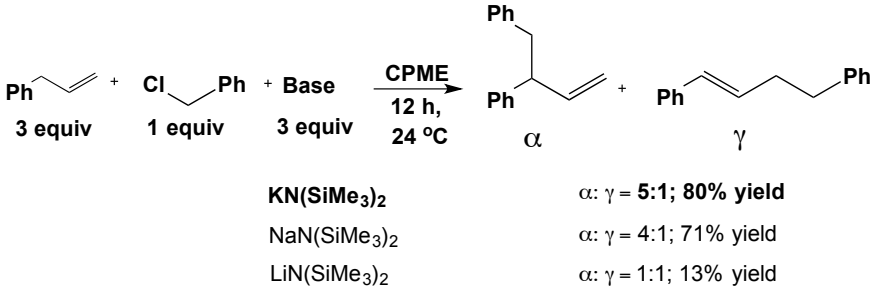
2. Results and Discussions:

2.1. Development of Room-Temperature Deprotonation/Benzylation of Allylbenzene.

Our first challenge was to identify conditions for the deprotonation of allylbenzene C(sp^3)–H bonds. The benzylic C−H bonds in allylbenzene have traditionally been deprotonated with *n*- and *sec*-BuLi at −78 °C or with *n*-BuMgCl.[15] These strong bases, however, are impractical for cross-coupling reactions because of their

limited compatibility with catalysts and coupling partners. We, therefore, focused on reversible in situ deprotonation of allylbenzene.

As a surrogate for the transmetallation step in the arylation reaction in Scheme 2, we substituted reaction of metallated allylbenzene with benzyl chloride (Scheme 3). To perform the benzylation, we screened 6 bases [$LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, $KN(SiMe_3)_2$, LiO*t*-Bu, NaO*t*-Bu and KO*t*-Bu] at room temperature in CPME (cyclopentylmethyl ether). As illustrated in Scheme 2, the bases leading to benzylation products were: $KN(SiMe_3)_2$ affording a 5:1 ratio of α:γ (80% yield), $NaN(SiMe_3)_2$ generating a 4:1 ratio (71% yield), and $LiN(SiMe_3)_2$ leading to a 1:1 ratio (13% yield). The α:γ ratios observed suggest that the nature of the metal plays a significant role in the regioselectivity.[16] None of the MO-*t*-Bu (M = Li, Na, K) bases generated detectable amounts of benzylation products. Unlike bases previously used to deprotonate allylbenzene (*n*- and *sec*-BuLi at −78 °C or *n*-Bu-MgCl), $MN(SiMe_3)_2$ has a high likelihood of compatibility with catalyst, reagents, and products in the DCCP (Scheme 2, left).



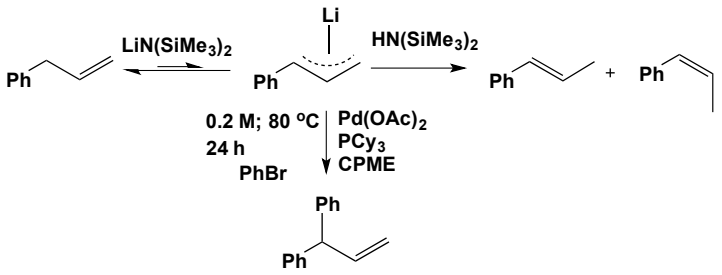
Scheme 3: Benzylation Used as Surrogate for the Transmetallation Step in DCCP.

2.2. Development and Optimization of Palladium-catalyzed DCCP of C(sp^3)−H of Allylbenzene.

We next turned our attention to catalyst identification for the DCCP of allylbenzene. We tested 29 sterically and electronically diverse mono- and bidentate phosphine ligands, 3 bases [$LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, $KN(SiMe_3)_2$] and different Pd(0) and Pd(II) precursors at 110 °C using the microscale high-throughput experimentation (HTE) techniques (see experimental section for details). Interestingly, the results of the HTE indicated the only base leading to the α-arylated product (**4a**) was $LiN(SiMe_3)_2$ (Table 1). Note that the main group metal is involved in both the deprotonation and the transmetallation steps in the arylation reaction. As such, the best base for the benzylation may not be the best for the palladium-catalyzed reaction. Of the 29 ligands examined, PCy_3 and Brettphos afforded very high regioselectivity in the coupling, giving exclusively the α-arylated products (see Supporting Information). NiXantphos, the only ligand that we found to perform well in the DCCP of diphenylmethane (pK_a = 32 in DMSO)[17] with aryl bromides,[3] gave a 2.6:1 ratio of α- and γ-arylated products. Because PCy_3 is less expensive than Brettphos,[18] we chose PCy_3 as the ligand for optimization of the arylation reaction.

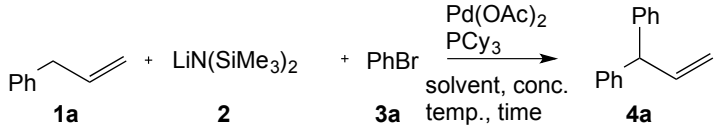
Translation of the microscale lead outlined above to laboratory scale (0.1 mmol) using 1 equiv of allylbenzene (**1a**), 3 equiv of aryl bromide (**2a**), 3 equiv of $LiN(SiMe_3)_2$, 5 mol % of $Pd(OAc)_2$ and 10 mol % of PCy_3 in CPME at 110 °C rendered the α-arylated product (**4a**) in 15% yield (entry 4, Table 1). Examination of four etheral solvents [THF, DME, dioxane and CPME] indicated that CPME was the best choice (entries 1–4, Table 1). During the optimization we observed the conversion of allylbenzene to *trans*-β-methylstyrene (major) and *cis*-β-methylstyrene (minor) (Scheme 4).[19] Unfortunately,

these isomers are less acidic than allyl benzene and do not undergo deprotonation under our conditions at 110 °C. Decreasing the temperature of the reaction to 80 °C increased the product yield to 30% (entry 5). Lowering of the temperature to 60 °C decreased the product yield to 20% (entry 6). Given the weak acidity of allylbenzene, and the resulting low concentration of the allyl anion, we increased the reaction concentration from 0.1 M to 0.2 M. At the higher concentration, the yield of α-arylated product (**4a**) increased to 40% (entry 7). We, therefore, increased the amount of allylbenzene to 3 equiv while using 3 equiv of $LiN(SiMe_3)_2$ and 1 equiv of bromobenzene at 0.2 M. The excess allylbenzene compensates for what appears to be an irreversible isomerization of some allylbenzene to unreactive b-methylstyrenes. Under these conditions, the α-arylated product (**4a**) was obtained in 65% yield (entry 8). Further increasing the concentration of the reaction mixture (0.3 M and 0.4 M) did not have an appreciable effect on the product yield (entries 9 and 10). We, therefore, chose 0.2 M as the reaction concentration. When 4 equiv of allylbenzene, 4 equiv of $LiN(SiMe_3)_2$ and 1 equiv of bromobenzene were used, the product was obtained in 74% yield (entry 11). Further optimization was performed by changing the ratio of PCy_3 with respect to the amount of palladium (entries 12 and 13). Finally, the arylation product (**4a**) was obtained in quantitative yield when employing $Pd(OAc)_2$ (5 mol %), PCy_3 (20 mol %) and a ratio of 4:4:1 of allylbenzene : $LiN(SiMe_3)_2$: bromobenzene at 80 °C for 24 h (entry 13).



Scheme 4*:* Isomerization of Allylbenzene to Unreactive β-Methylstyrenes.

Table 1: Optimization of Palladium-catalyzed DCCP of Allylbenzene.



entry	**1a:2:3a**	solvent	temp. (^{o}C)	conc. (M)	time. (h)	$Pd(OAc)_2$/ PCy_3 mol%	**4a**[a] (%)
1	1:3:3	THF	110	0.1	24	5/10	0
2	1:3:3	DME	110	0.1	24	5/10	0
3	1:3:3	Dioxane	110	0.1	24	5/10	10
4	1:3:3	CPME	110	0.1	24	5/10	15
5	1:3:3	CPME	80	0.1	24	5/10	30
6	1:3:3	CPME	60	0.1	24	5/10	20
7	1:3:3	CPME	80	0.2	24	5/10	40
8	3:3:1	CPME	80	0.2	24	5/10	65
9	3:3:1	CPME	80	0.3	24	5/10	68
10	3:3:1	CPME	80	0.4	24	5/10	69
11	4:4:1	CPME	80	0.2	24	5/10	74
12	4:4:1	CPME	80	0.2	24	5/15	80

13	4:4:1	CPME	80	0.2	24	5/20	>99

[a]Yield determined by ^{1}H NMR analysis of crude mixture with internal standard CH_2Br_2. Less than 4% of gamma-arylated product was detected by NMR.

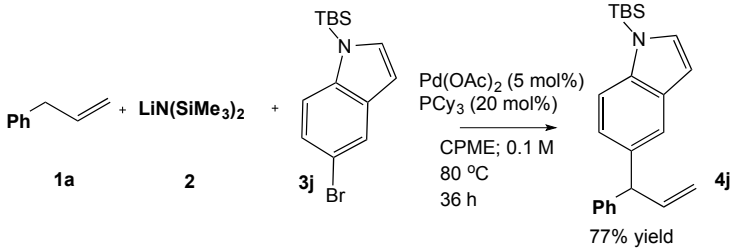
2.3. Scope of Aryl Bromides in Palladium-catalyzed DCCP of Allylbenzene.

With our optimized conditions (entry 13, Table 1), we examined the substrate scope of the arylation of allylbenzene with aryl bromides (Table 2). The DCCP showed excellent reactivity with aryl bromides possessing electron-donating groups (81–97% yields, entries 2–5). A range of other substrates exhibited good reactivity, including those with substituents in the *meta* (85% yield, entry 6) and *ortho* positions (83% yield, entry 7) as well as 1- and 2-bromo naphthalene (86 and 74% yields, entries 8 and 9). Nitrogen protected 5-bromoindole was also a good coupling partner and furnished the α-arylated product in 86% yield (entry 10).[20] The yields were typically lower, however, with electron-deficient aryl bromides (52–66%, entries 11 and 12). Ketones are well known to undergo 1,2-carbonyl addition reactions with reactive organometallics. Additionally, *p*-bromoacetophenone (p*K*a in DMSO is 24.7[21]) can participate in competitive aldol chemistry[22] and Pd-catalyzed α-arylation of the enolate under basic conditions.[23] Yet the a-arylated product **4m** derived from DCCP of allylbenzene was produced in reasonable yield (65%, entry 13). Acetals are known to undergo C–O cleavage with reactive organometallics,[24] however, the α-arylated product **4n** was produced in 87% yield (entry 14).

2.4. Scope of Aryl Bromides in Palladium-catalyzed DCCP of Allylarenes.

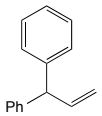
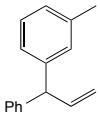
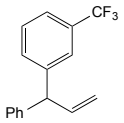
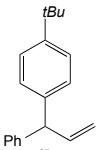
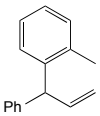
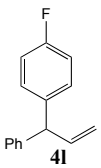
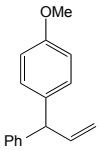
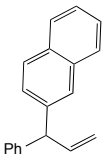
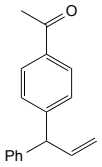
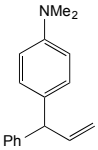
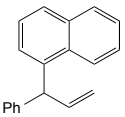
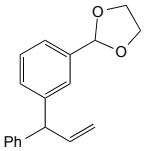
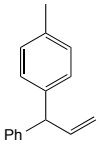
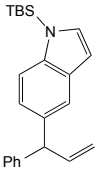
We next turned our attention to the allylbenzene scope (Table 3). Electron donating 4-allylanisole exhibited good reactivity (66–88% yields, entries 1–4). *Meta* substituted 3-allyl toluene furnished the desired coupling products in 80–91% yield (entries 5 and 6). Protected 5-bromoindole underwent the α-arylation with 3-allyltoluene in 82% yield (entry 7). *ortho*-Substituted 2-allyltoluene gave the desired product in 60% yield despite the additional steric hindrance at the α-center (entry 8). Electron-deficient 4-fluoro allylbenzene gave 64 and 66% yield with bromobenzene and protected 5-bromoindole (entries 9 and 10, respectively). 2- or 3-allylpyridine did not give the α-arylated products, but only underwent isomerization to the more stable vinyl pyridine derivatives. 2-Allylthiophene, on the other hand, underwent DCCP with 4-bromo *tert*-butylbenzene to afford the α-arylated product **4u** in 51% yield (entry 11). These systems are significantly more acidic than allyl benzenes and will require different catalysts to afford synthetically useful yields. It is noteworthy that excellent regioselectivity is observed in the substrates in Table 3, even when the steric and electronic parameters of the allylbenzene starting materials are varied.[10, 12]

When the DCCP with TBS protected bromoindole (**3j**) was scaled to 1 mmol with a ratio of 4:5:1 of **1a**:**2**:**3j** in the presence of 5 mol % $Pd(OAc)_2$ and 20 mol % PCy_3, the product **4j** was isolated in 77% yield (Scheme 5).



Scheme 5: Scaled up DCCP of Allylbenzene with TBS-Protected Bromoindole.

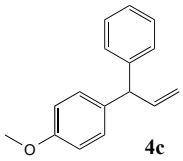
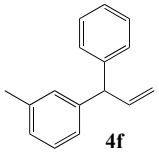
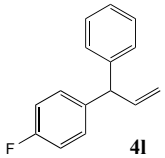
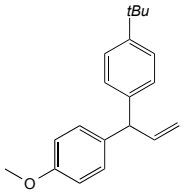
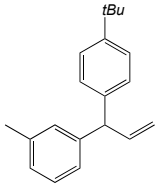
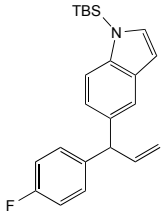
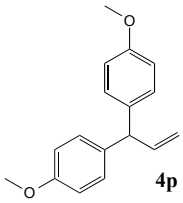
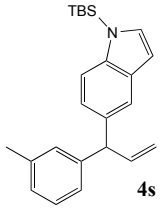
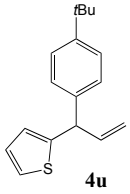
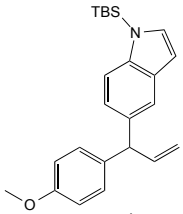
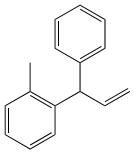
Table 2: Cross-Coupling of Allylbenzene with Aryl Bromides.[ii]

entry	product	yield (%)[a]	entry	product	yield (%)[a]	entry	product	yield (%)[a]
1	 **4a**	91[b]	6	 **4f**	85[c,d]	11	 **4k**	66[c,d]
2	 **4b**	88[b]	7	 **4g**	83[c,e]	12	 **4l**	52[b]
3	 **4c**	97[b]	8	 **4h**	86[c]	13	 **4m**	65[c,d]
4	 **4d**	81[b]	9	 **4i**	74[c]	14	 **4n**	87[c,d]
5	 **4e**	86[c]	10	 **4j**	86[c,d]			

[a] less than 4 % of the gamma products were detected by NMR and no Heck product was observed under our conditions. [b] 24 h. [c] 36 h. [d] 6 equiv of base used. [e] conc. is 0.3M

[ii] Co-author Dr. Gustavo Frensch also worked on evaluating the substrate scopes of products in Table 2.

Table 3: Cross-Coupling of Allylarenes with Aryl Bromides.[iii]

entry	product	yield (%)[a]	entry	product	yield (%)[a]	entry	product	yield (%)[a]
1	 **4c**	88	5	 **4f**	80[b]	9	 **4l**	64[b]
2	 **4o**	81	6	 **4r**	91	10	 **4t**	66
3	 **4p**	72	7	 **4s**	82	11	 **4u**	51[c]
4	 **4q**	66[b]	8	 **4g**	60[b]			

[a] reaction ran for 36 h. [b] 6 equiv of base used. [c] 5 eq of thiophene allyl and 3 equiv of base used; obtained product along with 12 % of linear products.

3. Conclusion:

In summary, we have developed the first direct α-arylation of unactivated allylbenzenes with aryl bromides via deprotonative cross-coupling processes. The significance of this work is it demonstrates that very weakly acidic hydrocarbon

[iii] Co-author Dr. Gustavo Frensch also worked on evaluating the substrate scopes of products in Table 3.

frameworks can be functionalized under DCCP conditions. The palladium-catalyzed arylation proceeded efficiently in the presence of PCy_3 and produces α-arylated 1,1-diarylprop-2-enes with very high regioselectivity (>95:5). It is noteworthy that our approach overrides the ubiquitous Heck reaction pathway by controlling the chemoselectivity. This is accomplished by use of a strong base, $LiN(SiMe_3)_2$, that reversibly deprotonates the allylbenzene. The lithiated allyl then undergoes transmetallation with the catalyst in a process that is faster than coordination and insertion of allylbenzene in the Heck pathway. The regiochemistry of the arylation is controlled by the ligand/palladium combination and is key to the success of this process. The fact that the α-arylated diarylallyl does not undergo base promoted isomerization to the more conjugated 1,1-diaryl-1-propene suggests that an enantioselective DCCP of allylbenzenes is possible and has inspired us to investigate this possibility.

Acknowledgements: I want to thank the co-authors of this allylbenzene project, Dr. Gustavo Frensch and Dr. Jiadi Zhang. Dr. G. Frensch was a visitng scholar from Brasil. I trained him in the chemistry experimental techniques for our deprotonative-cross-coupling (DCCP) projects. During his training, he helped me by evaluating some of the substrate scopes in Tables 2 and 3. I also thank Dr. Jiadi Zhang for running a few initial benzylation reactions, with $MN(SiMe_3)_2$ (M = K, Na, Li) bases, and arylation reactions of allylbenzene with bromobenzene.

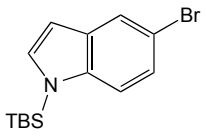
I also want to thank Dr. Ana Bellomo for training me on the High-Throughput Experimentation Techniques.

4. Experimental Section:

General Methods. All reactions were performed under nitrogen using oven-dried glassware and standard Schlenk or vacuum line techniques. Air- and moisture-sensitive solutions were handled under nitrogen and transferred via syringe. Anhydrous cyclopentyl methyl ether (CPME), dimethoxyethane (DME) and dioxane were purchased from Sigma-Aldrich and used as solvent without further purification. THF was dried over sodium benzophenone and triethylamine was distilled over calcium hydride and stored under nitrogen. Unless otherwise stated, reagents were commercially available and used as purchased without further purification. Chemicals were obtained from Sigma-Aldrich, Acros or Fisher Scientific, and solvents were purchased from Fisher Scientific. The progress of the reactions was monitored by thin- layer chromatography using WhatmanPartisil K6F 250 μmprecoated 60 Å silica gel plates and visualized by short-wave ultraviolet light as well as by treatment with ceric ammonium molybdate (CAM) stain. Silica gel (230–400 mesh, Silicycle) was used for flash chromatography. The ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR spectra were obtained using a Brüker AM-500 Fourier-transform NMR spectrometer at 500 and 125 MHz, respectively. Chemical shifts are reported in units of parts per million (ppm) downfield from tetramethylsilane (TMS), and all coupling constants are reported in hertz. The infrared spectra were obtained with KBr plates using a Perkin-Elmer Spectrum 100 Series FTIR spectrometer. High-resolution mass spectrometry (HRMS) data were obtained on a Waters LC-TOF mass spectrometer (model LCT-XE Premier) using chemical ionization (CI) or electrospray ionization (ESI)

in positive or negative mode, depending on the analyte. Melting points were determined on a Unimelt Thomas-Hoover melting point apparatus and are uncorrected.

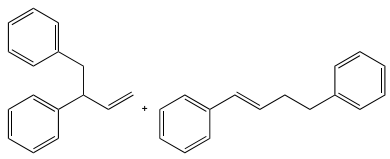
Preparation of Aryl Bromides:



5-Bromo-1-(*tert*-butyldimethylsilyl)-1*H*-indole (3j): Compound **3j** is prepared according to literature procedures.[25] The NMR spectral data match the previously published data.[25]

Procedures and Characterization for the Deprotonation/Benzylation of Allylbenzene.

General Procedure A: An oven-dried 10 mL reaction vial equipped with a stir bar was charged with $KN(SiMe_3)_2$ (0.3 mmol, 3 equiv) under a nitrogen atmosphere followed by 1 mL of dry CPME, and the reaction mixture was stirred for 5 min at 24 °C. Allylbenzene (0.3 mmol, 3 equiv) was added to the reaction mixture followed by benzyl chloride (0.1 mmol, 1 equiv). The reaction mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with three drops of H_2O, diluted with 1 mL of ethyl acetate, and filtered over a pad of silica. The pad was rinsed with additional ethyl acetate, and the solution was concentrated in vacuo. The crude material was loaded onto a silica gel column and purified by flash chromatography.



But-3-ene-1,2-diyldibenzene and (*E*)-but-1-ene-1,4-diyldibenzene: The reaction was performed following General Procedure A with allylbenzene (**1a**) (39.8 μL,

0.3 mmol), $KN(SiMe_3)_2$ (59.8 mg, 0.30 mmol) and benzyl chloride (11.5 μL, 0.1 mmol) in 1 mL of CPME at room temperature. The crude material was purified by flash chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 3:97) to give the product (16.7 mg, α:γ = 5:1, 80% yield) as a colorless oil. The NMR spectral data match the previously published data.[26]

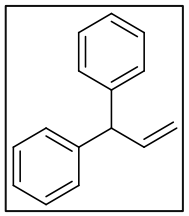
With NaHMDS: α:γ = 4:1, 71% yield.

With LiHMDS : α:γ = 1:1, 13% yield.

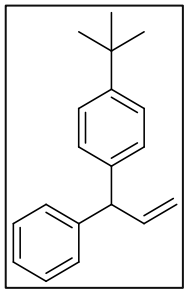
MO-*t*-Bu (M = K, Na, Li) = 0% (no reaction).

Procedure and Characterization for the Pd-Catalyzed DCCP of 1,1-diaryl-2-propenes.

General Procedure B: An oven-dried 10 mL reaction vial equipped with a stir bar was charged with $LiN(SiMe_3)_2$ (4 equiv) under a nitrogen atmosphere. A solution (from a stock solution) of $Pd(OAc)_2$ (5 mol%) and PCy_3 (20 mol%) in 1 mL of dry CPME was taken up by syringe and added to the reaction vial. After stirring for 5 min at 24 °C, allylarene (4 equiv) was added to the reaction mixture followed by aryl bromide (1 equiv). The reaction mixture was stirred for 24–36 h at 80 °C, cooled, quenched with three drops of H_2O, diluted with 1 mL of ethyl acetate, and filtered over a pad of silica. The pad was rinsed with additional ethyl acetate, and the solution was concentrated in vacuo. The crude material was loaded onto a silica gel column and purified by flash chromatography.

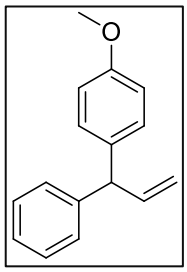


4a: Prop-2-ene-1,1-diyldibenzene. The reaction was performed following General Procedure B with allylbenzene (**1a**) (106 μL, 0.80 mmol, 4 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.80 mmol, 4 equiv) and bromobenzene (**3a**) (21 μL, 0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product (99% ^{1}H NMR yield with internal standard CH_2Br_2). The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 3:97) to give the product **4a** as a colorless oil (35.4 mg, 91% yield). The NMR spectral data match the previously published data.[27]

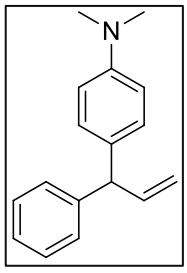


4b: 1-(*tert*-Butyl)-4-(1-phenylallyl)benzene. The reaction was performed following General Procedure B with allylbenzene (**1a**) (106 μL, 0.80 mmol, 4 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.80 mmol, 4 equiv) and 1-bromo-4-*tert*-butylbenzene (**3b**) (34.7 μL, 0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product (99% ^{1}H NMR yield with internal standard CH_2Br_2). The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 3:97) to give the product **4b** as a colorless oil (44.1 mg, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 –

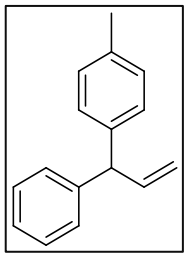
7.30 (m, 4H), 7.28 – 7.21 (m, 3H), 7.17 (dd, J = 9.5, 7.8 Hz, 2H), 6.41 – 6.27 (m, 1H), 5.32 – 5.19 (m, 1H), 5.04 (dt, J = 17.1, 1.5 Hz, 1H), 4.74 (d, J = 7.3 Hz, 1H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 143.7, 141.1, 140.4, 128.8, 128.6, 128.3, 126.5, 125.5, 116.3, 54.8, 34.6, 31.6; IR (neat) 3083, 3027, 2963, 2904, 2868, 1637, 1600, 1511, 1493, 918 cm^{-1}; HRMS *m/z* 235.1455 [$(M)^+$; calcd for $C_{19}H_{22}$: 235.1487].



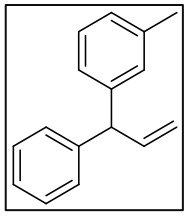
4c: 1-Methoxy-4-(1-phenylallyl)benzene. The reaction was performed following General Procedure B with allylbenzene (**1a**) (106 μL, 0.80 mmol, 4 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.80 mmol, 4 equiv) and 4-bromoanisole (**3c**) (25.0 μL, 0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product (99% ^{1}H NMR yield with internal standard CH_2Br_2). The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 3:97) to give the product **4c** as a colorless oil (43.5 mg, 97% yield). The NMR spectral data match the previously published data.[28]



4d: *N*, *N*-Dimethyl-4-(1-phenylallyl)aniline. The reaction was performed following General Procedure B with allylbenzene (**1a**) (106 μL, 0.80 mmol, 4 equiv), $LiN(SiMe_3)_2$ (200.8 mg, 1.2 mmol, 6 equiv) and 4-bromo-*N*,*N*-dimethylamine (**3d**) (40.0 mg, 0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product (86% ^{1}H NMR yield with internal standard CH_2Br_2). The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 5:95) to give the product **4d** as a colorless oil (38.5 mg, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.23 – 7.13 (m, 3H), 7.04 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 8.5 Hz, 2H), 6.33 – 6.22 (m, 1H), 5.17 (d, *J* = 10.1 Hz, 1H), 4.97 (d, *J* = 17.0 Hz, 1H), 4.64 (d, *J* = 7.2 Hz, 1H), 2.92 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.2, 144.0, 141.2, 131.3, 129.1, 128.5, 128.2, 126.0, 115.6, 112.7, 54.1, 40.7; IR (neat) 3080, 3025, 2926, 2800, 1635, 1613, 1519, 1449, 1349cm^{-1}; HRMS *m/z* 238.1596 [$(M+H)^+$; calcd for $C_{17}H_{20}N^+$: 238.1596].

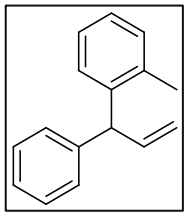


4e: 1-Methyl-4-(1-phenylallyl)benzene. The reaction was performed following General Procedure B with allylbenzene (**1a**) (106 μL, 0.80 mmol, 4 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.80 mmol, 4 equiv) and 4-bromotoluene (**3e**) (24.7 μL, 0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product (90% ^{1}H NMR yield with internal standard CH_2Br_2). The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 3:97) to give the product **4e** as a colorless oil (35.8 mg, 86% yield). The NMR spectral data match the previously published data.[28]

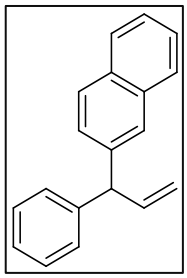


4f: 1-Methyl-3-(1-phenylallyl)benzene. The reaction was performed following General Procedure B with allylbenzene (**1a**) (106 μL, 0.80 mmol, 4 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.80 mmol, 4 equiv) and 3-bromotoluene (**3f**) (24.3 μL, 0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product (99% ^{1}H NMR yield with internal standard CH_2Br_2). The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 3:97) to give the

product **4f** as a colorless oil (35.4 mg, 85% yield). The NMR spectral data match the previously published data.[28]

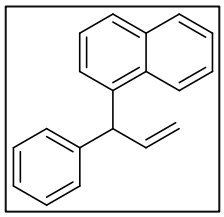


4g: 1-Methyl-2-(1-phenylallyl)benzene. The reaction was performed following General Procedure B with allylbenzene (**1a**) (159 μL, 1.2 mmol, 4 equiv), $LiN(SiMe_3)_2$ (300.0 mg, 1.8 mmol, 6 equiv) and 2-bromotoluene (**3g**) (37.0 μL, 0.3 mmol, 1 equiv) in 1 mL of CPME (0.3 M). The crude reaction mixture was filtered through a short pad of silica to afford the product (85% ^{1}H NMR yield with internal standard CH_2Br_2). The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 3:97) to give the product **4g** as a colorless oil (34.6 mg, 83% yield). The NMR spectral data match the previously published data.[28]

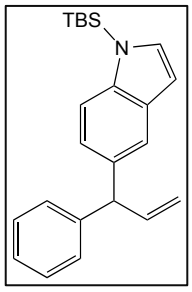


4h: 2-(1-Phenylallyl)naphthalene. The reaction was performed following General Procedure B with allylbenzene (**1a**) (106 μL, 0.80 mmol, 4 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.80 mmol, 4 equiv) and 2-bromonaphthalene (**3h**) (41.4 mg, 0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered

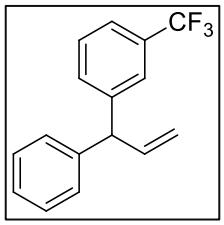
through a short pad of silica to afford the product (94% ^{1}H NMR yield with internal standard CH_2Br_2). The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 3:97) to give the product **4h** as a colorless oil (42.0 mg, 86% yield). The NMR spectral data match the previously published data.[28]



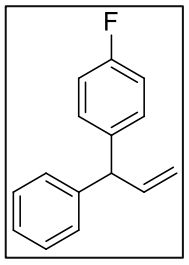
4i: 1-(1-Phenylallyl)naphthalene. The reaction was performed following General Procedure B with allylbenzene (**1a**) (106 μL, 0.80 mmol, 4 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.80 mmol, 4 equiv) and 1-bromonaphthalene (41.5 mg, 0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product (78% ^{1}H NMR yield with internal standard CH_2Br_2). The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 3:97) to give the product **4i** as a colorless oil (36.2 mg, 74% yield). The NMR spectral data match the previously published data.[29]



4j: 1-(*tert*-Butyldimethylsilyl)-6-(1-phenylallyl)-1*H*-indole. The reaction was performed following General Procedure B with allylbenzene (**1a**) (106 μL, 0.80 mmol, 4 equiv), $LiN(SiMe_3)_2$ (200.8 mg, 1.2 mmol, 6 equiv) and 5-bromo-1-(*tert*-butyldimethylsilyl)-1*H*-indole (**3j**) (62.1 mg, 0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 5:95) to give the product **4j** as a colorless oil (59.7mg, 86% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.39 (m, 2H), 7.35 – 7.23 (m, 4H), 7.21 (t, J = 7.1 Hz, 1H), 7.17 (d, J = 3.1 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 6.57 (d, J = 3.1 Hz, 1H), 6.40 (ddd, J = 17.1, 10.1, 7.3 Hz, 1H), 5.23 (d, J = 10.1 Hz, 1H), 5.03 (d, J = 17.1 Hz, 1H), 4.84 (d, J = 7.3 Hz, 1H), 0.93 (s, 9H), 0.60 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 145.6, 143.8, 138.8, 135.5, 135.3, 132.8, 132.4, 130.2, 126.6, 124.2, 119.8, 117.8, 108.9, 59.1, 30.4, 23.6, 0.06; IR (neat) 3080, 2954, 2929, 2884, 2858, 1636, 1600, 1520, 1470, 1446, 1290,1257, 1150cm^{-1}; HRMS *m/z* 348.2149 [$(M+H)^+$; calcd for $C_{23}H_{30}NSi^+$: 348.2148].

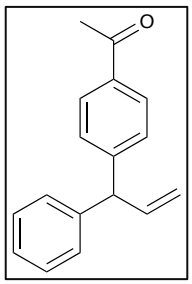


4k: 1-(1-Phenylallyl)-3-(trifluoromethyl)benzene. The reaction was performed following General Procedure B with allylbenzene (**1a**) (106 μL, 0.80 mmol, 4 equiv), $LiN(SiMe_3)_2$ (200.8 mg, 1.2 mmol, 6 equiv) and 3-bromo-benzotrifluoride (**3k**) (28 μL, 0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 3:97) to give the product **4k** as a colorless oil (34.6 mg, 66% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (m, 2H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.36 – 7.29 (m, 3H), 7.26 – 7.21 (m, 1H), 7.17 (d, *J* = 7.6 Hz, 2H), 6.37 – 6.16 (m, 1H), 5.27 (dd, *J* = 10.2, 0.9 Hz, 1H), 5.00 (dd, *J* = 17.1, 0.9 Hz, 1H), 4.75 (dd, *J* = 26.0, 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 142.2, 139.7, 132.0, 130.8 (q, *J* = 32 Hz), 128.8, 128.6, 128.5, 126.7, 125.2 (q, *J* = 3.8 Hz), 123.3 (q, *J* = 3.8 Hz), 117.1, 54.6; HRMS *m/z* 262.0956 [$(M)^+$; calcd for $C_{19}H_{22}$: 262.0969].

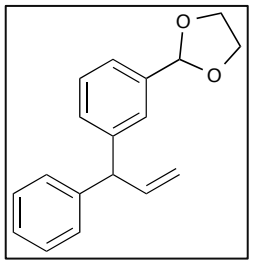


4l: 1-Fluoro-4-(1-phenylallyl)benzene. The reaction was performed following General Procedure B with allylbenzene (**1a**) (106 μL, 0.80 mmol, 4 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.80 mmol, 4 equiv) and 1-bromo-4-fluorobenzene (**3r**) (22 μL,

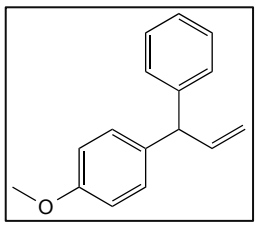
0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 3:97) to give the product **4l** as a colorless oil (22.1 mg, 52% yield). The NMR spectral data match the previously published data.[30]



4m: **1-(4-(1-Phenylallyl)phenyl)ethan-1-one**. The reaction was performed following General Procedure B with allylbenzene (**1a**) (106 μL, 0.80 mmol, 4 equiv), $LiN(SiMe_3)_2$ (200.8 mg, 1.2 mmol, 6 equiv) and *p*-bromo-acetophenone (**3m**) (28 µL, 0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 3:97) to give the product **4m** as a colorless oil (34.0 mg, 65% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, J = 6.6, 1.7 Hz, 2H), 7.34 – 7.23 (m, 4H), 7.21 (dd, J = 10.1, 4.1 Hz, 1H), 7.15 (dd, J = 13.7, 13.2 Hz, 2H), 6.28 (ddd, J = 17.2, 8.7, 5.5 Hz, 1H), 5.27 – 5.21 (m, 1H), 5.00 (dt, J = 17.1, 1.4 Hz, 1H), 4.77 (d, J = 7.1 Hz, 1H), 2.55 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.8, 149.0, 142.6, 139.9, 135.6, 129.0, 128.7, 128.7, 128.7, 126.8, 117.2, 55.1, 26.7; IR (neat) 3082, 3028, 3004, 2979, 2922, 2869, 1683, 1636, 1606, 1570, 1494, 1451, 1410, 1358, 1268, 1182 cm^{-1}; HRMS *m/z* 236.1196 [$(M+H)^+$; calcd for $C_{17}H_{16}O^+$: 236.1201].

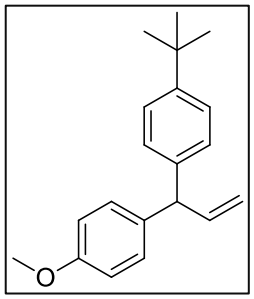


4n: **2-(3-(1-Phenylallyl)phenyl)-1,3-dioxolane**. The reaction was performed following General Procedure B with allylbenzene (**1a**) (106 μL, 0.80 mmol, 4 equiv), $LiN(SiMe_3)_2$ (200.8 mg, 1.2 mmol, 6 equiv) and 2-(3-bromophenyl)-1,3-dioxolane (**3n**) (28 μL, 0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 3:97) to give the product **4n** as a colorless oil (46.3 mg, 87% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.24 (m, 5H), 7.24 – 7.07 (m, 4H), 6.29 (ddd, J = 17.2, 10.1, 7.3 Hz, 1H), 5.77 (s, 1H), 5.21 (d, J = 10.1 Hz, 1H), 4.98 (d, J = 17.1 Hz, 1H), 4.74 (d, J = 7.1 Hz, 1H), 4.11 – 4.08 (m, 2H), 4.00 – 3.99 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 143.3, 140.7, 138.2, 129.7, 128.8, 128.7, 128.6, 126.8, 126.6, 124.7, 116.7, 104.0, 65.5, 55.1; IR (neat) 3080, 3027, 2977, 2886, 1636, 1600, 1492, 1451, 1386, 1224, 1158, 1098, 1079, 1030 cm^{-1}; HRMS *m/z* 267.1384 [$(M+H)^+$; calcd for $C_{18}H_{18}O_2^+$: 267.1385].



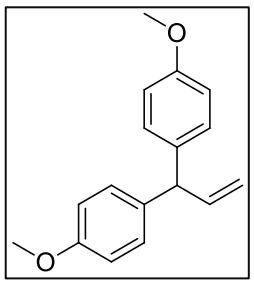
4c: 1-Methoxy-4-(1-phenylallyl)benzene. The reaction was performed following General Procedure B with 4-allylanisole (**1b**) (122.3 μL, 0.80 mmol,

4 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.80 mmol, 4 equiv) and bromobenzene (**3a**) (21 μL, 0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product (99% ^{1}H NMR yield with internal standard CH_2Br_2). The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 3:97) to give the product **4c** as a colorless oil (39.5 mg, 88% yield). The NMR spectral data match the previously published data.[28]

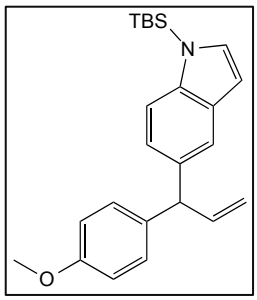


4o: 1-(*tert*-Butyl)-4-(1-(4-methoxyphenyl)allyl)benzene. The reaction was performed following General Procedure B with 4-allylanisole (**1b**) (122.3 μL, 0.80 mmol, 4 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.80 mmol, 4 equiv) and 1-bromo-4-*tert*-butylbenzene (**3b**) (34.7 μL, 0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product (86% ^{1}H NMR yield with internal standard CH_2Br_2). The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 3:97) to give the product **4o** as a colorless oil (45.4 mg, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 2H), 7.14 – 7.09 (m, 4H), 6.87 – 6.82 (m, 2H), 6.29 (ddd, J = 17.2, 10.1, 7.3 Hz, 1H), 5.19 (dt, J = 10.1, 1.4 Hz, 1H), 4.99 (dt, J = 17.0, 1.5 Hz, 1H), 4.66 (d, J = 7.4 Hz, 1H), 3.80 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (125

MHz, $CDCl_3$) δ 158.3, 149.3, 141.4, 140.8, 135.9, 129.7, 128.3, 125.5, 116.0, 114.0, 55.5, 54.0, 34.6, 31.6; IR (neat) 3080, 3024, 2962, 2858, 1637,1510, 1464, 1247, 1176cm^{-1}; HRMS *m/z* 281.1919 [$(M+H)^+$; calcd for $C_{20}H_{25}O^+$: 281.1905].

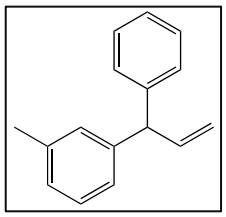


4p: 4,4'-(Prop-2-ene-1,1-diyl)bis(methoxybenzene). The reaction was performed following General Procedure B with 4-allylanisole (**1b**) (122.3 μL, 0.80 mmol, 4 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.80 mmol, 4 equiv) and 4-bromoanisole (**3c**) (25 μL, 0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product (76% ^{1}H NMR yield with internal standard CH_2Br_2). The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 3:97) to give the product **4p** as a colorless oil (36.6 mg, 72% yield). The NMR spectral data match the previously published data.[31]



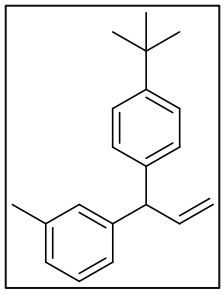
4q: 1-(*tert*-Butyldimethylsilyl)-5-(1-(4-methoxyphenyl)allyl)-1*H*-indole. The reaction was performed following General Procedure B with 4-allylanisole

(**1b**) (122.3 μL, 0.80 mmol, 4 equiv), $LiN(SiMe_3)_2$ (200.8 mg, 1.2 mmol, 6 equiv) and 5-bromo-1-(*tert*-butyldimethylsilyl)-1*H*-indole (**3j**) (62.1 mg, 0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 5:95) to give the product **4q** as a colorless oil (49.8 mg, 66% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.43 (m, 2H), 7.21 – 7.16 (m, 3H), 7.01 (dd, *J* = 8.6, 1.7 Hz, 1H), 6.89 – 6.85 (m, 2H), 6.58 (d, *J* = 3.2 Hz, 1H), 6.39 (ddd, *J* = 17.2, 10.1, 7.3 Hz, 1H), 5.22 (d, *J* = 10.1 Hz, 1H), 5.04 (dt, *J* = 17.1, 1.5 Hz, 1H), 4.81 (d, *J* = 7.2 Hz, 1H), 3.81 (s, 3H), 0.96 (s, 9H), 0.61 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 141.9, 139.8, 136.4, 135.1, 131.5, 131.2, 129.7, 122.6, 120.1, 115.5, 113.7, 113.7, 104.8, 55.3, 54.2, 26.34, 19.50, -3.97; HRMS *m/z* 378.2253 [$(M+H)^+$; calcd for $C_{19}H_{22}$: 378.2253].

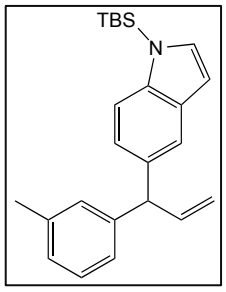


4f: 1-Methyl-3-(1-phenylallyl)benzene. The reaction was performed following General Procedure B with 1-allyl-3-methylbenzene (**1c**) (121.1 μL, 0.80 mmol, 4 equiv), $LiN(SiMe_3)_2$ (200.8 mg, 1.2 mmol, 6 equiv) and bromobenzene (**3a**) (21 μL, 0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes =

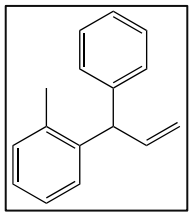
3:97) to give the product **4f** as a colorless oil (33.3 mg, 80% yield). The NMR spectral data match the previously published data.[28]



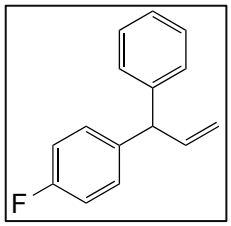
4r: 1-(1-(4-(*tert*-Butyl)phenyl)allyl)-3-methylbenzene. The reaction was performed following General Procedure B with 1-allyl-3-methylbenzene (**1c**) (121.1 μL, 0.80 mmol, 4 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.80 mmol, 4 equiv) and 1-bromo-4-tert-butylbenzene (**3b**) (34.7 μL, 0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 3:97) to give the product **4r** as a colorless oil (48.1 mg, 91% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 2H), 7.26 – 7.22 (m, 1H), 7.21 – 7.15 (m, 2H), 7.12 – 7.02 (m, 3H), 6.35 (ddd, J = 17.4, 10.1, 7.4 Hz, 1H), 5.25 (dt, J = 10.1, 1.3 Hz, 1H), 5.06 (dt, J = 17.0, 1.4 Hz, 1H), 4.71 (d, J = 7.4 Hz, 1H), 2.37 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.2, 143.6, 141.1, 140.5, 138.1, 129.5, 128.5, 128.3, 127.3, 125.8, 125.5, 116.1, 54.8, 34.6, 31.6, 21.7; IR (neat) 3080, 3024, 2962, 2904, 2866, 1637, 1605, 1515, 1487, 918 cm^{-1}; HRMS *m/z* 264.1876 [$(M)^+$; calcd for $C_{20}H_{24}$: 264.1878].



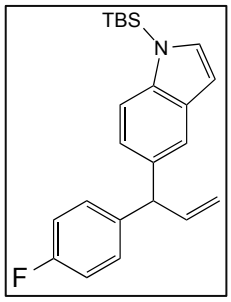
4s: 1-(*tert*-Butyldimethylsilyl)-6-(1-(m-tolyl)allyl)-1*H*-indole. The reaction was performed following General Procedure B with 1-allyl-3-methylbenzene (**1c**) (121.1 μL, 0.80 mmol, 4 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.80 mmol, 4 equiv) and 5-bromo-1-(*tert*-butyldimethylsilyl)-1*H*-indole (**3j**) (62.1 mg, 0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 5:95) to give the product **4s** as a colorless oil (59.3 mg, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 1.7 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 1H), 7.24 – 7.19 (m, 1H), 7.18 (d, *J* = 3.2 Hz, 1H), 7.13 – 6.98 (m, 4H), 6.61 – 6.57 (m, 1H), 6.42 (ddd, *J* = 17.3, 10.1, 7.4 Hz, 1H), 5.26 – 5.20 (m, 1H), 5.05 (dt, *J* = 17.0, 1.6 Hz, 1H), 4.82 (d, *J* = 7.4 Hz, 1H), 2.34 (s, 3H), 0.96 (s, 9H), 0.60 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.9, 145.4, 143.5, 141.6, 138.7, 135.2, 135.0, 133.2, 131.9, 130.7, 129.5, 126.3, 123.9, 119.4, 117.5, 108.6, 58.8, 30.1, 25.3, 23.3, -0.2; IR (neat) 3080, 3018, 2954, 2928, 2857, 1636, 1605, 1516, 1467, 1362, 1290,1257, 1148cm^{-1}; HRMS *m/z* 362.2312 [$(M+H)^+$; calcd for $C_{24}H_{32}NSi^+$: 362.2307].



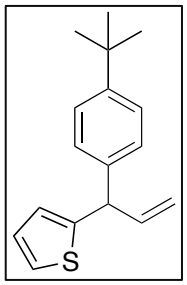
4g: 1-Methyl-2-(1-phenylallyl)benzene: The reaction was performed following General Procedure B with 1-allyl-2-methylbenzene (**1e**) (118.2 μL, 0.80 mmol, 4 equiv), $LiN(SiMe_3)_2$ (200.8 mg, 1.2 mmol, 6 equiv) and bromobenzene (**3a**) (21 μL, 0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 3:97) to give the product **4g** as a colorless oil (25.0 mg, 60% yield). The NMR spectral data match the previously published data. [28]



4l: 1-Fluoro-4-(1-phenylallyl)benzene. The reaction was performed following General Procedure B with 1-allyl-4-fluorobenzene (**1d**) (108 μL, 0.80 mmol, 4 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.80 mmol, 4 equiv) and bromobenzene (**3a**) (21 μL, 0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 3:97) to give the product **4l** as a colorless oil (27.2 mg, 64% yield). The NMR spectral data match the previously published data.[30]



4t: 1-(*tert*-Butyldimethylsilyl)-6-(1-(4-fluorophenyl)allyl)-1*H*-indole. The reaction was performed following General Procedure B with 1-allyl-4-fluorobenzene (**1d**) (108 μL, 0.80 mmol, 4 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.80 mmol, 4 equiv) and 5-bromo-1-(*tert*-butyldimethylsilyl)-1*H*-indole (**3j**) (62.1 mg, 0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 5:95) to give the product **4t** as a colorless oil (48.3 mg, 66% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 2H), 7.19 – 7.14 (m, 3H), 6.98 – 6.91 (m, 3H), 6.54 (d, J = 3.1 Hz, 1H), 6.37 – 6.28 (m, 1H), 5.19 (d, J = 10.2 Hz, 1H), 5.00 – 4.95 (m, 1H), 4.79 (d, J = 7.2 Hz, 1H), 0.91 (s, 9H), 0.57 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3 (d, J = 250 Hz), 141.3, 139.8 (d, J = 3.8 Hz), 139.7, 134.4, 131.4 (d, J = 12.5 Hz), 130.1, 130.0, 122.3, 120.0, 115.8, 115.0 (d, J = 21 Hz), 113.7, 104.6, 54.1, 26.2, 19.4, -4.0; HRMS *m/z* 366.2062 [$(M)^+$; calcd for $C_{23}H_{29}NSiF^+$: 366.2053].



4u: **2-(1-(4-(*tert*-Butyl)phenyl)allyl)thiophene**: The reaction was performed following General Procedure B with allylthiophene (**1u**) (124.0 mg, 1.0 mmol, 5 equiv), $LiN(SiMe_3)_2$ (100.4 mg, 0.6 mmol, 3 equiv) and 1-bromo-4-*tert*-butylbenzene (**3b**) (34.7 μL, 0.2 mmol, 1 equiv) in 1 mL of CPME (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 3:97) to give the product **4n** as a colorless oil (26.0 mg, 51% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 2H), 7.21 – 7.14 (m, 3H), 6.94 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.82 – 6.75 (m, 1H), 6.36 – 6.20 (m, 1H), 5.19 (dd, *J* = 10.0, 1.0 Hz, 1H), 5.10 (dt, *J* = 16.9, 1.3 Hz, 1H), 4.88 (d, *J* = 7.5 Hz, 1H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.5, 147.4, 140.3, 139.8, 127.6, 126.6, 125.3, 124.8, 124.0, 115.9, 50.1, 34.4, 31.3; IR (neat) 3080, 2962, 2905, 2867, 1637, 1512, 1463, 1436, 1409, 1364, 1229, 1109 cm^{-1}; HRMS *m/z* 256.1290 [$(M+H)^+$; calcd for $C_{17}H_{20}S^+$: 256.1286].

Representative Microscale High-Throughput Experimentation for Base & Catalyst Identification.

General Experimental: The experimental procedures in this work were similar to those

reported.[32] Parallel synthesis was accomplished in an MBraun glovebox operating with a constant N_2-purge (oxygen typically <5 ppm). The experimental design was accomplished using Accelrys Library Studio. Screening reactions were carried out in 1 mL vials (30 mm height ×8 mm diameter) in a 96-well plate aluminum reactor block. Liquid chemicals were dosed using multi-channel or single-channel pipettors. Solid chemicals were dosed manually as solutions or slurries in appropriate solvents. Undesired additional solvent was removed using a GeneVac system located inside the glovebox. The reactions were heated and stirred on a heating block with a tumble-stirrer (V&P Scientific) using 1.98 mm diameter ×4.80 mm length parylene stir bars. The tumble stirring mechanism helped to insure uniform stirring throughout the 96-well plate. The reactions were sealed in the 96-well plate during reaction. Below each reactor vial in the aluminum 96-well plate was a 0.062 mm thick silicon-rubber gasket. Directly above the glass vial reactor tops was a Teflon perfluoroalkoxy copolymer resin sealing gasket and above that, two more 0.062 mm thick silicon-rubber gaskets. The entire assembly was compressed between an aluminum top and the reactor base with 9 evenly-placed screws.

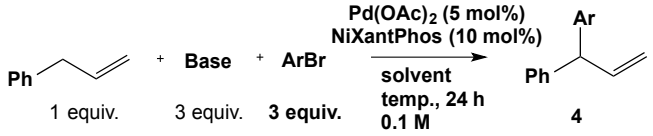
Set up:

Experiments were set up inside a glovebox under a nitrogen atmosphere. A 96-well aluminum block containing 1 mL glass vials was predosed manually with $Pd(OAc)_2$ (0.5 μmol) and PCy_3 (1 μmol) in THF. The solvent was evacuated to dryness using a GeneVac vacuum centrifuge, and $LiN(SiMe_3)_2$ (30 μmol) in THF was added to the ligand/catalyst mixture. The solvent was removed on the GeneVac, and a parylene stir bar was then added to each reaction vial. bromobenzene (30 μmol/reaction), allylbenzene (10 μmol/reaction) were then dosed together into each reaction vial as a solution in CPME

(100 μL, 0.1 M). The 96-well plate was then sealed and stirred for 24 h at 110 °C.

Work up: Upon opening the plate to air, di-*t*ert-butylbenzene (used as an internal standard to measure HPLC yields) (1 μmol/reaction) in 500 μL of acetonitrile was syringed into each vial. The plate was then covered again and the vials stirred for 10 min to extract the product and to ensure good homogenization. Into a separate 96-well LC block was added 700 μL of acetonitrile, followed by 40 μL of the diluted reaction mixtures. The LC block was then sealed with a silicon-rubber storage mat, and mounted on HPLC instrument modified with an autosampler for analysis.

(1) First Screening:



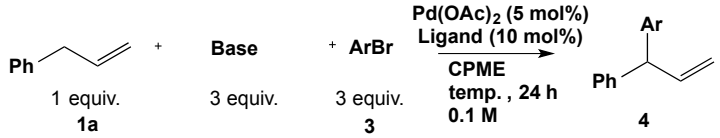
Bases: 3 bases [$KN(SiMe_3)_2$, $NaN(SiMe_3)_2$, $LiN(SiMe_3)_2$] were screened.

Solvents: 4 solvents [CPME, Dioxane, THF and DME] were screened.

Temperatures: 80 and 110 °C.

The lead hit from the first screen was the combination of $Pd(OAc)_2$ (5 mol%), NiXantPhos (10 mol%), $LiN(SiMe_3)_2$, CPME at 80 °C, which translated into 40% yield in a 2.6:1 ratio of α- and γ-arylated products on laboratory scale.

(2) Second Screening:



a) 3 bases [$KN(SiMe_3)_2$, $NaN(SiMe_3)_2$, $LiN(SiMe_3)_2$] were screened.

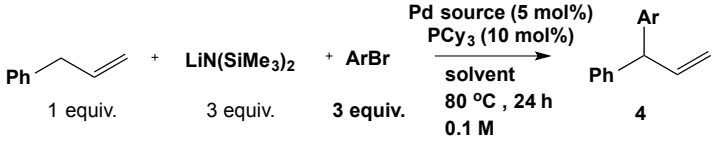
b) **Ligand** was used in a 4:1 ratio relative to Pd for monodentate ligands and 2:1 ratio for bidentate ligands.

$Pd(OAc)_2$ (5 mol %) was used to test 29 sterically and electronically diverse, mono- and bidentate phosphine ligands (ligands 1-29 from the Table below).

Temperatures: 80 and 110 °C.

The lead hit from the second screen was the combination of $Pd(OAc)_2$ (5 mol%), PCy_3 (10 mol%), $LiN(SiMe_3)_2$, CPME at 80 °C, which translated into 30% yield on laboratory scale.

(3) Third Screening:



b) **Pd sources:** 6 Pd sources [$Pd(OAc)_2$, $Pd(PCy_3)_2$, $Pd(PPh_3)_4$, $(\eta^3\text{-}C_3H_5)_2Pd_2Cl_2$, $Pd(cod)Cl_2$, and $Pd(dba)_2$] were screened.

c) **Solvents**: 4 solvents [CPME, Dioxane, THF and DME] were screened.

The lead hit from the third screen was the combination of $Pd(OAc)_2$ (5 mol %), PCy_3 (10 mol %), $LiN(SiMe_3)_2$ in CPME at 80°C, which translated into 30% yield on laboratory scale.

	Ligand libraries(1 – 17)	4a/IS	γ–selective Product/IS
1	2-Dicyclohexylphosphino-2',6'-di-i-propoxy-1,1'-biphenyl (RuPhos)	0.0	0.0
2	5-(Di-*t*-butylphosphino)-1', 3', 5'-triphenyl-1'H-[1,4']bipyrazole (BippyPhos)	0.17	0.0
3	2-Dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (SPhos)	0.0	0.0
4	2-(Dicyclohexylphosphino)biphenyl (Cy-JohnPhos)	0.0	0.0
5	2-(Di-*t*-butylphosphino)-3-methoxy-6-methyl-2',4',6'-tri-i-propyl-1,1'-biphenyl (RockPhos)	0.42	0.55
6	2-(Dicyclohexylphosphino)-2'-methylbiphenyl (MePhos)	0.66	0.0
7	1-[2-[Bis(*t*-butyl)phosphino]phenyl]-3,5-diphenyl-1H-pyrazole (TrippyPhos)	0.0	0.0
8	Dicyclohexyl-[3,6-dimethoxy-2-(2,4,6-triisopropylphenyl)phenyl]phosphane (BrettPhos)	1.93	0.0
9	9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (Xantphos)	0.57	0.0
10	4,6-Bis(diphenylphosphino)phenoxazine (NiXantphos)	0.78	0.71
11	Tri-*t*-butyl phosphonium tetrafluoroborate	0.1	0.0
12	Tricyclohexylphosphonium tetrafluoroborate	1.73	0.0
13	*N*-phenyl-2-(di-*t*-butylphosphino)pyrrole (cataCXium PtB)	0.0	0.0
14	1-(2,4,6-Trimethylphenyl)-2-(dicyclohexylphosphino)imidazole (cataCXium PICy)	0.3	0.0
15	Di-*t*-butyl-[1-(2-methoxyphenyl)pyrrol-2-yl]phosphane (cataCXium POMetB)	0.0	0.0
16	*N*-phenyl-2-(dicyclohexylphosphino)pyrrole (cataCXium PCy)	0.0	0.0
17	Di(1-adamantyl)-n-butylphosphine (CatCXium A)	0.0	0.0

	Ligand libraries(18 – 29)	4a/IS	γ–selective Product/IS
18	Di(1-adamantyl)-2-morpholinophenylphosphine (MorDalPhos)	0.0	0.0
19	2-(Di-*t*-butylphosphino)-2'-methylbiphenyl (*t*Bu-MePhos)	0.0	0.0
20	1,1'-Bis(diphenylphosphino)ferrocene (dppf)	0.0	0.4
21	1,1'-Bis(di-*t*-butylphosphino)ferrocene (dtbpf)	0.0	0.0
22	1,1'-Bis(diisopropylphosphino)ferrocene (dippf)	0.0	0.0
23	2-Dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl (XPhos)	0.0	0.0
24	1,2,3,4,5-Pentaphenyl-1'-(di-*t*-butylphosphino)ferrocene (QPhos)	0.0	0.0
25	Tri-*o*-tolylphosphine	0.27	0.0
26	Triphenylphosphine (PPh_3)	0.0	0.0
27	(*S*)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl ((*S*)-BINAP)	0.0	0.1
28	2-Dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl (DavePhos)	0.0	0.0
29	2-(Di-*t*-butylphosphino)biphenyl (JohnPhos)	0.0	0.0

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CHAPTER 2
Palladium-catalyzed C(sp^3)–H Arylation of *N*-Boc Benzylalkylamines[i]

1. Introduction:

Diarylmethylamines represent an important class of chemical compounds that has significant potential in pharmaceutical sciences. Diarylmethylamines are core structures of Zyrtec,[1] Levocetirizine,[2] Meclozine,[3] Solifenacin,[4] BDF9148,[5] SNC80,[6] and ARM434 (Figure 1).[7] Generally, the synthesis of diarylmethylamines involves nucleophilic addition of organometallic reagents to imines.[8] More recently, functionalization of sp^3-hybridized C–H bonds adjacent to nitrogen has emerged as a powerful methodology for the formation of C–C bonds.[9] For instance, Li and coworkers have developed a method in the functionalization of sp^3 C–H bonds adjacent to nitrogen in amines via cross-dehydrogenative coupling processes.[9]

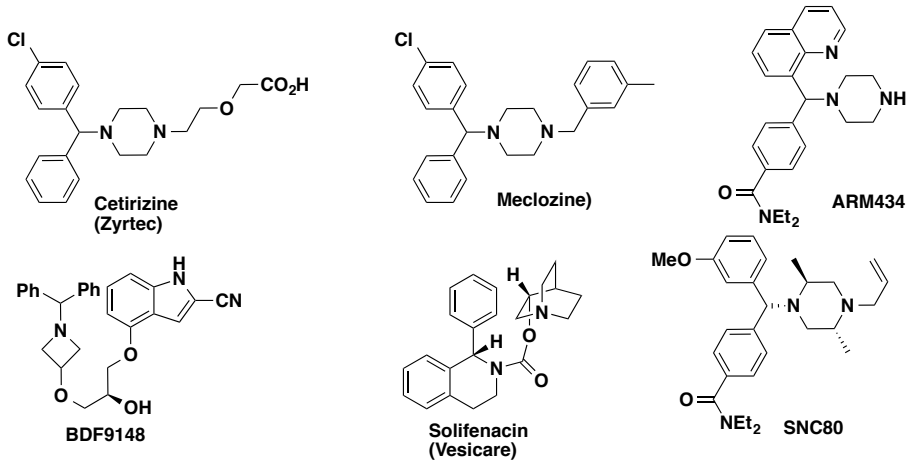
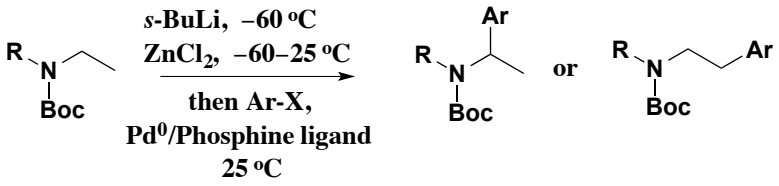


Fig 1: Important diarylmethylamine containing molecules.

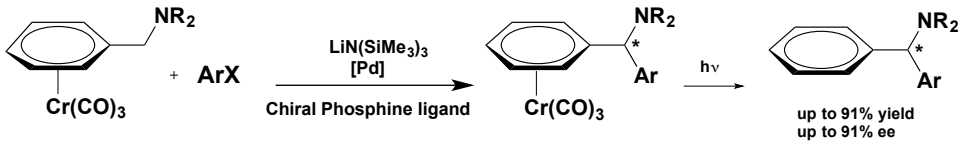
[i] This project was initiated by Byeong-Seon Kim, a final year graduate student at Walsh group. This manuscript is in preparation.

Direct deprotonation of the benzylic C–H bonds in secondary benzylamine derivatives under catalytic conditions is very challenging. This result is due to the weak acidity of sp^3-hybridized benzylic C–H bonds adjacent to nitrogen,[10] which generally requires strong bases, such as alkyl lithiums for deprotonation.[11] The resulting lithiated benzylmethylamine species were then captured with a variety of electrophiles.[11, 12] These strong bases, however, are impractical for cross-coupling reactions due to their limited compatibility with catalysts and coupling partners. To circumvent this issue, Baudoin,[13] Knochel,[14] Campos,[15] and Dieter[16] have established two-step methods that commence with direct lithiation of secondary amines with *s*-BuLi followed by *in situ* transmetallation to zinc, boron, or copper and subsequent coupling to aryl halides. However, this two-step approach requires the use of strong bases and very low temperatures (-78 °C), making it operational less practical (Scheme 1).



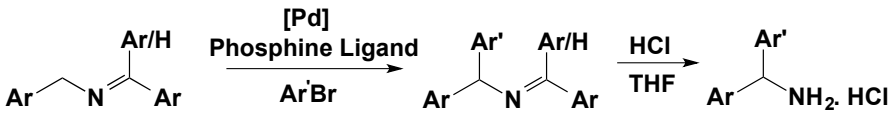
Scheme 1: Ligand-controlled α/β-Arylation of Boc-protected Acyclic Amines.

To avoid the use of strong bases at low temperatures, we, therefore, focused on reversible *in situ* deprotonation of benzylalkylamines. We previously introduced a novel approach toward the catalytic synthesis of diarylmethylamines based on an η^6-arene-activation strategy to decrease the p*Ka* of benzylic C–H bonds.[17, 18] The corresponding diarylmethylamines were obtained in excellent yields and enantioselectivities (Scheme 2).



Scheme 2: Synthesis of Diarylmethylamines based on an η^6-Arene-Activation Strategy.

Nevertheless, the stoichiometric use of chromium precludes large-scale application of the chemistry. We therefore, focused on a chromium-free direct arylation of benzylic C(sp^3)–H bonds. One such strategy for the synthesis of diarylmethylamines relies on the generation and reactions of 2-azaallyl anions. This strategy was introduced by Oshima[19] and optimized by Buchwald[20] and by us[21] and takes the advantage of stability of 2-azaallyl anions supported by aminofluorenes, ketimines, or aldimines to yield protected primary amines (Scheme 3).

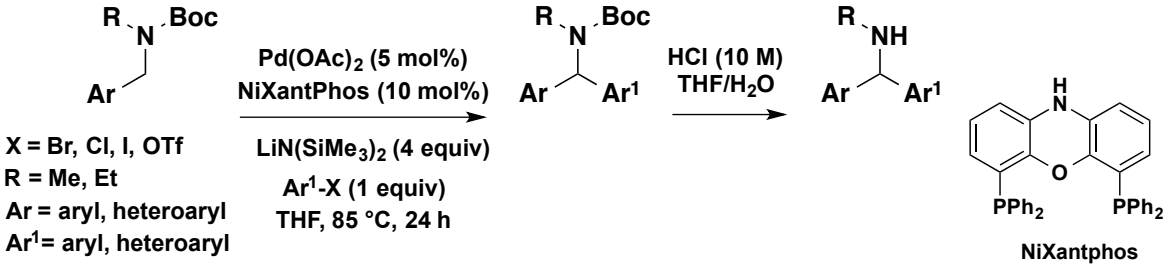


Scheme 3: Cross-coupling *N*-Benzyl Benzophenone Ketimines/Aldimines.

Considering the importance of diarylmethylamines in medicinal chemistry, we envisioned the reversible and directed deprotonation of *N*-Boc benzylalkylamine at the benzylic C–H bonds under catalytic conditions. The Boc group was chosen for its ability to both increase the acidity of the benzylic C–H bonds and coordinate to the base and facilitate deprotonation.

We, therefore, envisioned the direct cross-coupling using Boc-protected benzylalkylamines with aryl halides by a deprotonative cross-coupling process (DCCP), a program that we have recently developed for the functionalization of weakly acidic sp^3-hybridized C–H bonds by palladium catalysis. Substrates that have been successfully functionalized using this approach including diarylmethanes,[22, 23] phosphine oxides,[24] benzoxazoles,[25] sulfoxides,[26] sulfones,[27] sulfides,[28] amides,[29] allylbenzenes, [30] and chromium-activated benzylic amines (to produce enantioenriched diarylmethylamines). [17]

Here we report the first direct cross-coupling of Boc-protected benzylalkylamines with aryl electrophiles to provide Boc-protected diarylmethylamines in moderate to high yields (40-93%, 29 examples). Upon removal of Boc group, secondary diarylmethylamines are also generated (75-95% yields, 2 substrates) (Scheme 4).



Scheme 4: Palladium-Catalyzed DCCP of *N*-Boc Benzylalkylamines followed by Deprotection to generate Diarylmethylamines.

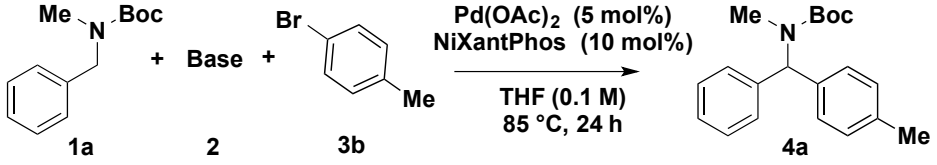
2. Results and Discussions:

2.1. Development and Optimization of Palladium-catalyzed DCCP of C(sp^3)− H of Benzylmethylamines.

As is commonly the case of deprotonative cross-coupling processes (DCCP),[22, 23] a base for the reversible deprotonation must be identified and a catalyst chosen that is compatible with the basic reaction conditions. Based on our experience with DCCP of weakly acidic substrates (p*K*a 25–35), we chose van Leeuwen's NiXantPhos ligand as a starting point.[23, 24] To identify a suitable base for the deprotonation of the weakly acidic sp^3-hybridized C-H bond adjacent to nitrogen, we screened 6 bases [$LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, $KN(SiMe_3)_2$, Li*O*t-Bu, Na*O*t-Bu and K*O*t-Bu] with $Pd(OAc)_2$/NiXantphos system at 85 ºC in cyclopentylmethyl ether (CPME) for 24 h. As illustrated in Table 1, the bases leading to arylation products were the $MN(SiMe_3)_2$ (M = Li, Na, K) bases, affording 10-40% yield of the diarylmethylamines in CPME (entries 1–3). None of the MO-*t*-Bu (M = Li, Na, K) bases generated detectable amounts of arylated products (entries 4-6). Examination of four ethereal solvents [THF, DME, dioxane and CPME] indicated that THF was the best choice (entry 9; 99% assay yield). In order to optimize the reaction conditions with the NiXantPhos/$Pd(OAc)_2$ system, we examined different ratios of the benzylmethylamine pro-nucleophile, arylbromide, $LiN(SiMe_3)_2$ at different reaction temperatures (50 and 80 ºC). When 3 equiv of benzylmethylamine, 3 equiv of $LiN(SiMe_3)_2$ or $NaN(SiMe_3)_2$ and 1 equiv of ArBr were used in THF, the desired arylated product was obtained in quantitative yield (entries 9 and 10). $KN(SiMe_3)_2$, on the other hand, gave the **4a** product only in 21% yield (entry 11). Furthermore, decreasing the reaction temperature from 80 to 50 °C had a detrimental effect on the yield, resulting in a drop of **4a** from 99 % to 20% yield (entry 12).

Although the combination of $Pd(OAc)_2$ and NiXantphos as precatalyst afforded the diarylmethylamine product **4a** in excellent yield, the use of 3 equiv of *N*-Boc benzylmethylamine (entries 9 and 10) was suboptimal. Reducing the equivalents of the benzylmethylamine pro-nucleophile from 3 to 1 equiv in THF at 80 °C resulted in a drop in product **4a** from >95% to 61%, along with 30% unreacted *N*-Boc benzylmethylamine **1a** (entry 13). Changing base from $LiN(SiMe_3)_2$ to $NaN(SiMe_3)_2$ also resulted in a drop in yield of **4a** to 57% (entry 15). The best result was obtained when 1.1 equiv of *N*-Boc benzylmethylamine, 1 equiv of 4-bromotoluene **3a**, and 4 equiv of $LiN(SiMe_3)_2$ at 85 °C were used in THF for 24 h, producing the product **4a** in 99% assay yield and 88% isolated yield (entry 16).

Table 1: Optimization of *N*-Boc Benzylmethylamine Arylation Reaction.[ii]



Entry	Base	**1a:2:3b**	Solvent	Y[a] [%]
1	$LiN(SiMe_3)_2$	3:3:1	CPME	40
2	$NaN(SiMe_3)_2$	3:3:1	CPME	30
3	$KN(SiMe_3)_2$	3:3:1	CPME	10
4	LiO*t*Bu	3:3:1	CPME	–

[ii] Reactions 1, 2, and 3 in Table 1 were performed by Byeong-Seon Kim.

5	NaO*t*Bu	3:3:1	CPME	–
6	KO*t*Bu	3:3:1	CPME	–
7	$LiN(SiMe_3)_2$	3:3:1	Dioxane	15
8	$LiN(SiMe_3)_2$	3:3:1	DME	10
9	$LiN(SiMe_3)_2$	3:3:1	THF	99
10	$NaN(SiMe_3)_2$	3:3:1	THF	99
11	$KN(SiMe_3)_2$	3:3:1	THF	21
12	$LiN(SiMe_3)_2$	3:3:1	THF	20[b]
13	$LiN(SiMe_3)_2$	1:3:3	THF	61[c(i)]
14	$LiN(SiMe_3)_2$	1:3:1	THF	74[c(ii)]
15	$NaN(SiMe_3)_2$	1:3:3	THF	57[c(iii)]
16	$LiN(SiMe_3)_2$	1.1:4:1	THF	99 (88)[d]

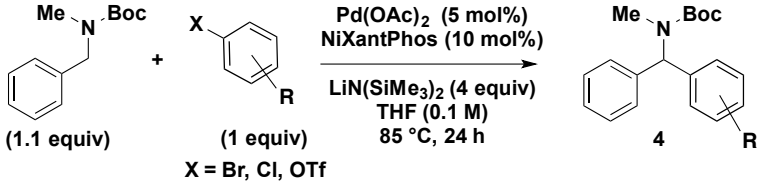
[a] Yield determined by ^{1}H NMR analysis of unpurified reaction mixture with internal standard CH_2Br_2. [b] reaction at 50 °C. [c] i. ii. iii. 30%, 20%, and 18% of unreacted **1a** left respectively. [d] isolated yield.

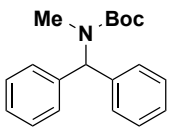
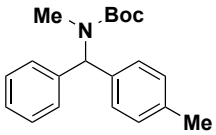
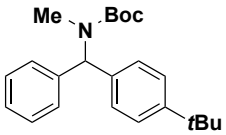
2.2. Scope of *N*-Boc Benzylmethylamine 1a with Aryl Electrophiles in Palladium-catalyzed DCCP.

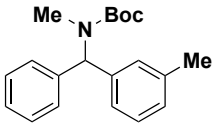
With best conditions identified (entry 16, Table 1), we sought to evaluate the substrate scope of the arylation of *N*-Boc benzylmethylamine **1a** with aryl electrophiles

(Table 2). The DCCP showed good to excellent reactivity with various aryl electrophiles, such as aryl halides and an aryl triflate. The arylated products were obtained in moderate to excellent yields for *para*, *meta* and *ortho* alkyl-substitued aryl halides and the aryl triflate (50–91%, **4b**-**4e**, Table 2). 1–Bromonaphthalene was also a good coupling partner, furnishing **4f** in 78% yield. Aryl halides bearing 3-methoxy and 3-*N,N*-dimethylamine groups furnished the coupling products **4g** and **4h** in 64% and 93% yields, respectively. Electron rich 4-bromoanisole also exhibited good reactivity, yielding the coupling product **4l** in 87% yield. The yields were lower, however, with 1-bromide and 1-chloride, 4-fluorobenzene, giving **4j** in 70 and 60% yields, respectively. Acetals are known to undergo C–O bond cleavage with reactive organometallics,[32] however, the product **4k** was produced in 68% yield. The arylated product was obtained in excellent yield with heterocyclic 4-chlorophenyl pyrrole, giving **4l** in 93% yield. The yield was lowered with nitrogen protected 5-bromoindole, which furnished the heterocyclic product **4m** in 50% yield.

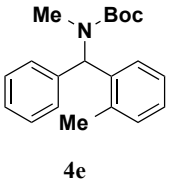
Table 2. Cross-Coupling of *N*-Boc Benzylmethylamine with Aryl Electrophiles.



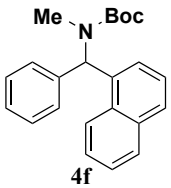
		
4a	**4b**	**4c**
90% (X = Br) 88% (X = Cl)	88% (X = Br) 78% (X = I)	90% (X = Br) 91% (X = OTf)



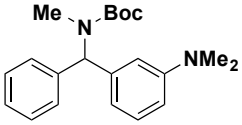
4d
86% (X = Br)



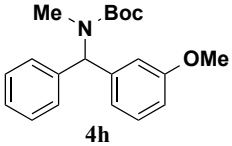
4e
50% (X = Br)



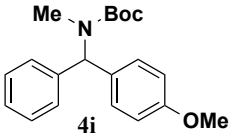
4f
78% (X = Br)



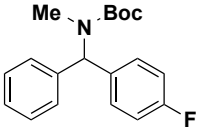
4g
93% (X = Br)



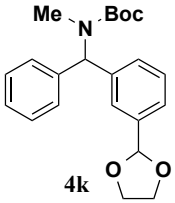
4h
64% (X = Br)



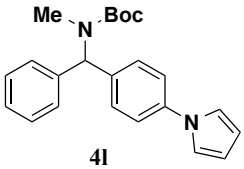
4i
87% (X = Br)
85% (X = Cl)



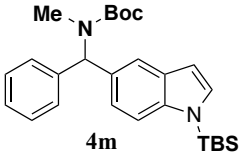
4j
70% (X = Br)
60% (X = Cl)



4k
68% (X = Br)



4l
93% (X = Cl)



4m
50% (X = Br)

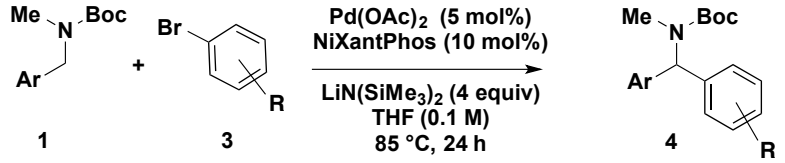
[a] isolated yield.

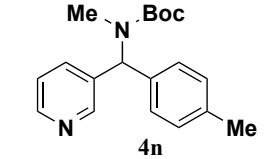
2.3. Scope of *N*-Boc Benzylmethylamine Derivatives in Palladium-catalyzed DCCP.

We next turned our attention to the scope of *N*-Boc benzylmethylamine derivatives (Table 3). Heterocyclic *N*-Boc methyl(pyridin-3-methyl)amine exhibited good reactivity with alkyl-substituted, electron-donating and electron-deficient aryl bromides (**4n**-**4p**, 72–88% yield). The benzylmethylamine bearing a 3–OMe substituent furnished the desired products in 57-90% yield (**4h**, **4q**, and **4r**). 1-Naphthalene substituted benzylmethylamine also afforded products in 57-80% yield (**4h**, **4q**, and **4r**). 4-Fluoro *N*-Boc benzylmethylamine coupled with 4-bromotoluene and 4-bromoanisole in 73 and

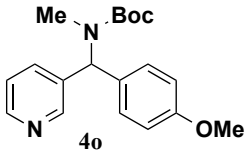
76% yields (**4j** and **4v**), respectively. When the methyl group on *N*-Boc benzylmethylamine was changed to *N*-ethyl group, the cross-coupling arylated products were obtained in 75 and 60% yields with 4-bromotoluene and 4-bromoanisole, respectively (**4w** and **4x**, Table 3).

Table 3. Cross-Coupling of *N*-Boc Benzylalkylamines with Aryl Bromides.

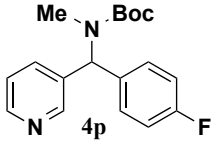




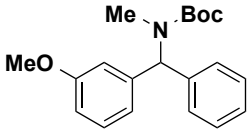
4n
98%



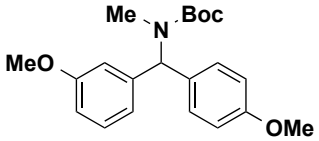
4o
88%



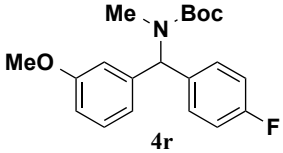
4p
72%



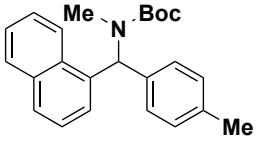
4h
90%



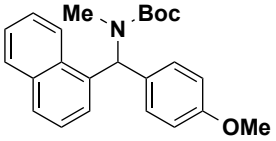
4q
87%



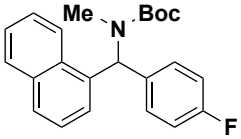
4r
57%



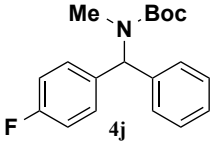
4s
70%



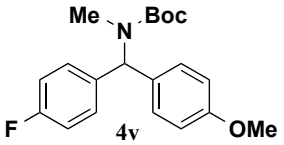
4t
57%



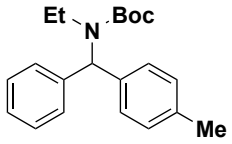
4u
80%[a]



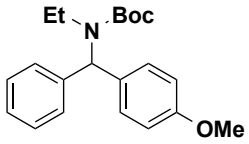
4j
76%



4v
73%



4w
75%

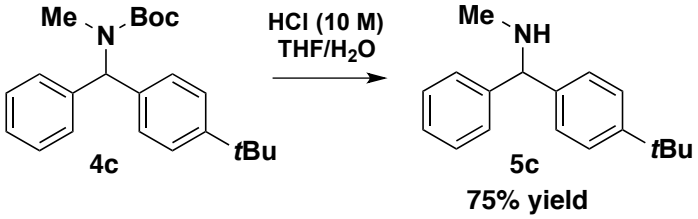


4x
60%

[a] 10/20 mol% of Pd and NiXantphos used.

Unfortunately, reactions with 2-thiophene, 2-furyl, 2- and 4-pyridyl containing hetero-benzylmethylamines did not yield detectable amounts of coupling products. This is not totally unexpected given that these systems are significantly more acidic than *N*-Boc benzylmethylamine and will likely require different catalysts for to the desired products.

The Boc-protected **4c** was treated with 10 M hydrochloric acid followed by basic work up to provide 2° free 1-(4-(*tert*-butyl)phenyl)-*N*-methyl-1-phenylmethanamine **5c** in 75% yield (Scheme 5).



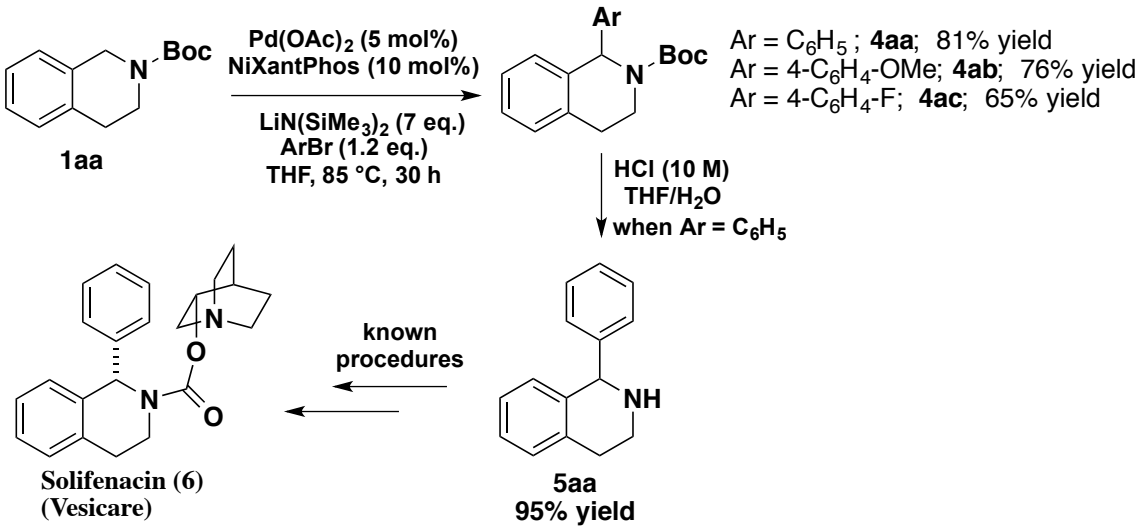
Scheme 5: Deprotection of Boc Group to Provide 1-(4-(*tert*-Butyl)phenyl)-*N*-methyl-1-phenylmethanamine **5c**.

2.4. Synthesis of 1-Phenyl-1,2,3,4-tetrahydroisoquinoline, a Key Intermediate in the Synthesis of Solifenacin by DCCP.

To increase the utility of our method, we extended our method to the synthesis of 1-phenyl-1,2,3,4-tetrahydroisoquinoline (**5aa**), a key intermediate for the antimuscarinic

agent Solifenacin (Scheme 6).[33] Solifenacin (**6**), in the form of succinate salt, is commericialized as Vesicare, a medication that has been used for the treatement of urinary frequency, urinary incontinence, or urinary associated with overactive bladder (OAB).[33] 1-Arylated-1,2,3,4-tetrahydroisoquinolines (**5aa**) have also been studied for their anti-HIV activities.[34] Given the great importance of **5aa** in medicinal chemistry, we wanted to investigate the direct deprotonation of the benzylic C–H bonds in *N*-Boc protected 1,2,3,4-tetrahydroisoquinoline (**1aa**, Scheme 6).

Under our DCCP conditions, the cross-coupling of **1x** took place smoothly to provide **4aa** in 81% isolated yield (Scheme 6). The arylated tetrahydroisoquinoline products derived from 4-bromoanisole and 1-bromo-4-fluorobenzene were obtained in 76 and 65% yields, respectively (**4ab** and **4ac,** Scheme 6). For the synthesis of the key intermediate (**5aa**), the arylated product (**4aa**) was deprotected with HCl to provide 1-phenyl-1,2,3,4-tetrahydroisoquinoline **5aa** in 95% yield. Racemic **5aa** has been used in the synthesis of Solifenacin (**6**, Scheme 6).[35]



Scheme 6: Cross-coupling of *N*-Boc-1,2,3,4-tetrahydroisoquinoline (**1aa**), and Formal Synthesis of 1-Phenyl-1,2,3,4-tetrahydroisoquinoline (**5aa**), a Key Intermediate for Solifenacin (**6**).

3. Conclusion:

In conclusion, we have developed the first direct α-arylation of *N*-Boc benzylalkylamines with aryl electrophiles by using the deprotonative cross-coupling processes. The significance of this work is it demonstrates that very weakly acidic hydrocarbon frameworks can be functionalized under DCCP conditions. Key to the success of this approach is the NiXantphos-based catalyst that enables the arylation to be conducted under mild conditions and the identification of a hindered base [$LiN(SiMe_3)_2$] that promoted the C–H deprotonation under the catalytic cross-coupling conditions.

Acknowledgements: I want to thank Byeong-Seon Kim, a final year graduate student in Walsh group, for initiating this project, while I was working with benzyl carbonate derivatives. I later took over the project to further optimize the reaction conditions and to examine the substrate scopes of the arylation reaction of *N*-Boc benzylalkylamines with aryl electrophiles.

4. Experimental Section:

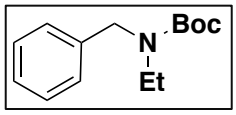
General Methods. All reactions were performed under nitrogen using oven-dried glassware and standard Schlenk or vacuum line techniques. Air- and moisture-sensitive solutions were handled under nitrogen and transferred via syringe. Anhydrous cyclopentyl methyl ether (CPME), dimethoxyethane (DME) and dioxane were purchased from Sigma-Aldrich and used as solvent without further purification. THF was dried over sodium benzophenone and triethylamine was distilled over calcium hydride and stored under nitrogen. Unless otherwise stated, reagents were commercially available

and used as purchased without further purification. Chemicals were obtained from Sigma-Aldrich, Acros or Fisher Scientific, and solvents were purchased from Fisher Scientific. The progress of the reactions was monitored by thin-layer chromatography using WhatmanPartisil K6F 250 μmprecoated 60 Å silica gel plates and visualized by short-wave ultraviolet light as well as by treatment with ceric ammonium molybdate (CAM) stain. Silica gel (230–400 mesh, Silicycle) was used for flash chromatography. The ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were obtained using a Brüker AM-500 Fourier-transform NMR spectrometer at 500 and 125 MHz. Chemical shifts are reported in units of parts per million (ppm) downfield from tetramethylsilane (TMS), and all coupling constants are reported in hertz. The infrared spectra were obtained with KBr plates using a Perkin-Elmer Spectrum 100 Series FTIR spectrometer. High-resolution mass spectrometry (HRMS) data were obtained on a Waters LC-TOF mass spectrometer (model LCT-XE Premier) using chemical ionization (CI) or electrospray ionization (ESI) in positive or negative mode, depending on the analyte. Melting points were determined on a Unimelt Thomas-Hoover melting point apparatus and are uncorrected.

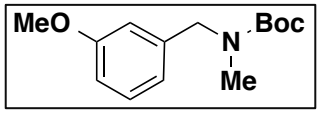
Procedures and Characterization of *tert*-butyl (aryl-methyl)(methyl)carbamates:

General Procedure A: To a solution of *tert*-butyl (aryl-methyl)(methyl)carbamate in CH_2Cl_2 (10 mL) at 0 °C was added di-*tert*-butyl dicarbonate dropwise. The reaction mixture was allowed to warm to room temperature, and stirring was continued for 12 h. The crude reaction mixture was filtered through a short pad of silica, and the solvent was removed under reduced pressure. The crude product was further purified by flash column chromatography on silica gel.

***tert*-Butyl benzyl(methyl)carbamate (1a):** The reaction was performed following General Procedure A with benzylmethylamine (1.29 mL, 10 mmol, 1.2 equiv) and di-*tert*-butyl dicarbonate (1.91 mL, 8.33 mmol, 1 equiv). The crude reaction mixture was filtered through a short pad of silica to afford the product (>95% purity by ^{1}H NMR). The crude material was used without further purification to give the product **1a** as a colorless oil (2.12 g, 96% yield). The NMR spectral data match the previously published data.[13]

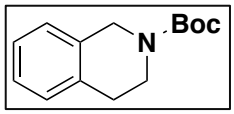


***tert*-Butyl benzyl(ethyl)carbamate (1b):** The reaction was performed following General Procedure A with benzylethylamine (0.74 mL, 5 mmol, 1.0 equiv) and di-*tert*-butyl dicarbonate (1.26 mL, 5.05 mmol, 1.05 equiv). The crude reaction mixture was filtered through a short pad of silica to afford the product (>95% purity by ^{1}H NMR). The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **1b** as a colorless oil (1.11 g, 94% yield). The NMR spectral data match the previously published data.[13]

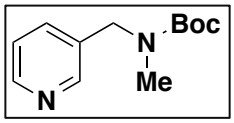


***tert*-Butyl (3-methoxybenzyl)(methyl)carbamate (1c):** The reaction was performed

following General Procedure A with 1-(3-methoxyphenyl)-*N*-methylmethanamine (0.48 mL, 3 mmol, 1.0 equiv) and di-*tert*-butyl dicarbonate (0.76 mL, 3.3 mmol, 1.1 equiv). The crude reaction mixture was filtered through a short pad of silica to afford the product (>95% purity by ^{1}H NMR). The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **1c** as a colorless oil (0.73 g, 96% yield). The NMR spectral data match the previously published data.[36] ^{1}H NMR ($CDCl_3$) δ 7.24 (t, J=7.8 Hz, 1H), 7.24 (m, 3H), 4.40 (s, 2H), 3.80 (s, 3H), 2.82 (br s, 3H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 159.8, 139.8, 129.5, 119.6, 112.9, 112.6, 79.6, 55.1, 52.5, 33.9, 28.4; IR (neat) 2900, 1680, 1600, 1420, 1280, 1040, 870, 760 cm^{-1}; HRMS: m/z 251.1503 [$(M)^+$; calcd for $C_{14}H_{21}NO_3^+$: 251.1521].

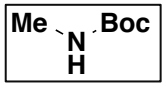


***tert*-Butyl 3,4-dihydroisoquinoline-2(1*H*)-carboxylate (1aa):** The reaction was performed following General Procedure A with 1,2,3,4-tetrahydroisoquinoline (0.75 mL, 6 mmol, 1.0 equiv) and di-*tert*-butyl dicarbonate (1.45 mL, 6.05 mmol, 1.05 equiv). The crude reaction mixture was filtered through a short pad of silica to afford the product (>95% purity by ^{1}H NMR). The crude material was used without further purification to give **1aa** as a colorless oil (1.3 g, 96%). The NMR spectral data match the previously published data.[37]



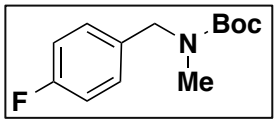
***tert*-Butyl methyl(pyridin-3-ylmethyl)carbamate (1d):** The reaction was first performed following General Procedure A with pyridin-3-ylmethanamine (0.51 mL, 5 mmol, 1.0 equiv) and di-*tert*-butyl dicarbonate (1.21 mL, 5.1 mmol, 1.05 equiv). The crude reaction mixture was filtered through a short pad of silica to afford the product (>95% purity by ^{1}H NMR). The crude material was used without further purification to give *tert*-butyl (pyridin-3-ylmethyl)carbamate as a colorless oil (2.0 g, 95%).

NaH (0.77 g, 19.2 mmol, 2.0 equiv) (60 % dispersion in mineral oil) was added portionwise to a solution of *tert*-butyl methylcarbamate (2.0 g, 9.6 mmol, 1 equiv) in THF (15 mL) and then was stirred for 1.5 hour at room temperature. Iodomethane (1.2 mL, 19.2 mmol, 2.0 equiv) was then added dropwise to the previous solution at 0°C. The reaction mixture was allowed to warm to room temperature, and stirring was continued for 12 h. The crude reaction mixture was filtered through a short pad of silica, and the solvent was removed under reduced pressure. The crude product was further purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **1d** as a colorless oil (1.9 g, 88% yield). The NMR spectral data match the previously published data.[13]

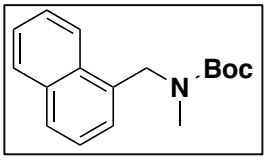


***tert*-Butyl methylcarbamate (1e):** A solution of methylamine (2.22 mL, 20 mmol, 1 equiv, 40% in water) in CH_2Cl_2 was cooled to 0 °C and di-*tert*-butyl dicarbonate (5.8 mL, 16.7 mmol, 1 equiv) was added dropwise. The reaction mixture stirred for 10 minutes,

warmed to room temperature, and stirring was continued for 12 h. The crude reaction mixture was filtered through a short pad of silica, and the solvent was removed under reduced pressure. The crude material was then used without further purification to give *tert*-butyl methylcarbamate as a colorless oil (2.5 g, 97%). The NMR spectral data match the previously published data.[38]



***tert*-Butyl (4-fluorobenzyl)(methyl)carbamate (1f):** KH (0.27 g, 6.6 mmol, 1.1 equiv) (98 % dispersion in mineral oil) was added portionwise to a solution of *tert*-butyl methylcarbamate **1e** (0.79 g, 6 mmol, 1 equiv) in THF (10 mL) and then was stirred for 1.5 hour at room temperature. 1-(bromomethyl)-4-fluorobenzene (0.81 mL, 6.6 mmol, 1.1 equiv) was added dropwise to the previous solution at 0°C. The reaction mixture was allowed to warm to room temperature, and stirring was continued for 12 h. The crude reaction mixture was filtered through a short pad of silica, and the solvent was removed under reduced pressure. The crude product was further purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **1f** as a colorless oil (1.30 g, 82% yield). The NMR spectral data match the previously published data.[13]



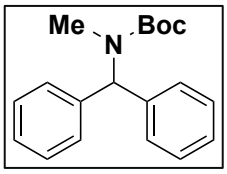
***tert*-Butyl methyl(naphthalen-1-ylmethyl)carbamate (1g):** NaH (0.14 g, 6.0 mmol,

1.2 equiv) (60 % dispersion in mineral oil) was added portionwise to a solution of *tert*-butyl methylcarbamate **1e** (0.66 g, 5 mmol, 1 equiv) in THF (10 mL) and then was stirred for 1.5 hour at room temperature. 1-(chloromethyl)naphthalene (1.06 g, 6.0 mmol, 1.2 equiv) was added dropwise to the previous solution at 0°C. The reaction mixture was allowed to warm to room temperature, and stirring was continued for 20 h. The crude reaction mixture was filtered through a short pad of silica, and the solvent was removed under reduced pressure. The crude product was further purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **1g** as a colorless oil (1.09 g, 80% yield).). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, 1H, rotomer), 7.86 (d, *J* = 7.0 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.55 – 7.46 (m, 2H), 7.42 (m, *J* = 7.0 Hz, 1H), 7.31 (s, 1H), 4.91 (s, 2H), 2.78 (d, 3H, rotomer), 1.55 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, rotomers) δ 155.8, 133.8, 133.3, 131.6, 128.6, 128.1, 126.3, 125.8, 125.0, 124.0, 123.1, 79.7, 50.2, 33.5, 28.5; IR 3048, 3005, 2975, 2930, 2873, 1694, 1599, 1512, 1480, 1455, 1393, 1366, 1250, 1165, 1144 cm^{-1}; HRMS *m/z* 271.1572 [$(M)^+$; calcd for $C_{17}H_{21}NO_2^+$: 271.1578].

Procedures and Characterization of the Pd-Catalyzed DCCP of *N*-Boc Diarylmethylamines:

General Procedure B: An oven-dried 10 mL reaction vial equipped with a stir bar was charged with $LiN(SiMe_3)_2$ (4 equiv) under a nitrogen atmosphere. A solution (from a stock solution) of $Pd(OAc)_2$ (5 mol%) and NiXantphos (10 mol%) in 1 mL of dry THF was taken up by syringe and added to the reaction vial. After stirring for 5 min at 24 °C, *N*-Boc benzylalkylamine (1.1 equiv) was added to the reaction mixture followed by aryl

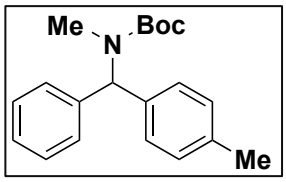
bromide (1 equiv). Note that the aryl bromide in a solid form was added to the reaction vial prior to $LiN(SiMe_3)_2$. The reaction mixture was stirred for 24–36 h at 85 °C, cooled, quenched with three drops of H_2O, diluted with 1 mL of diethyl ether, and filtered over a pad of silica. The pad was rinsed with additional diethyl ether, and the solution was concentrated in vacuo. The crude material was loaded onto a silica gel column and purified by flash chromatography.



***tert*-Butyl-benzhydryl(methyl)carbamate (4a):** The reaction was performed following General Procedure B with *N*-Boc benzylmethylamine (**1a**) (24.3 mg, 0.11 mmol, 1.1 equiv), $LiN(SiMe_3)_2$ (66.9 mg, 0.4 mmol, 4 equiv) and aryl halide (0.1 mmol, 1 equiv) in 1 mL of THF (0.1 M). The crude reaction mixture was filtered through a short pad of silica to afford the product (>95% ^1H NMR yield with internal standard CH_2Br_2). The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4a** as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, J = 7.6 Hz, 4H), 7.27 (t, J = 6.8 Hz, 2H), 7.18 (d, J = 7.3 Hz, 4H), 6.58 (s, 1H), 2.68 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 139.8, 128.5, 128.2, 127.1, 79.8, 30.9, 28.4 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR (neat) 3460, 3028, 2965, 2927, 1692, 1494, 1452, 1366, 1309, 1142, 1021 cm^{-1}; HRMS *m/z* 320.1634 [$(M+Na)^+$; calcd for $C_{19}H_{23}NO_2Na^+$: 320.1626].

With PhBr: Mass & Yield of **4a** = 28.0 mg, 90%.

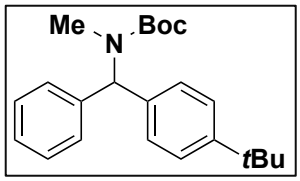
With PhCl: Mass & Yield of **4a** = 27.1 mg, 87%.



***tert*-Butyl-methyl(phenyl(*p*-tolyl)methyl)carbamate (4b):** The reaction was performed following General Procedure B with *N*-Boc benzylmethylamine (**1a**) (24.3 mg, 0.11 mmol, 1.1 equiv), $LiN(SiMe_3)_2$ (66.9 mg, 0.4 mmol, 4 equiv) and aryl halide (0.1 mmol, 1 equiv) in 1 mL of THF (0.1 M). The crude reaction mixture was filtered through a short pad of silica to afford the product (>95% ^{1}H NMR yield with internal standard CH_2Br_2). The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4b** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 2H), 7.28 (d, *J* = 7.1 Hz, 1H), 7.21 – 7.17 (m, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.07 (d, *J* = 7.8 Hz, 2H), 6.55 (s, 1H), 2.67 (s, 3H), 2.35 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 140.0, 136.9, 136.7, 129.0, 128.7, 128.5, 128.3, 127.1, 79.9, 30.9, 28.5, 21.1 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR (neat) 3464, 3060, 2975, 2928, 1693, 1513, 1494, 1389, 1256, 1170, 1142, 1021 cm^{-1}; HRMS *m/z* 334.1783 [$(M+Na)^+$; calcd for $C_{20}H_{25}NO_2Na^+$: 334.4142].

With bromotoluene: Mass & Yield of **4b** = 27.4 mg, 88%.

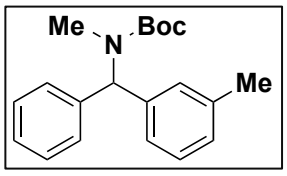
With iodotoluene: Mass & Yield of **4b** = 27.1 mg, 87%.



***tert*-Butyl-((4-(*tert*-butyl)phenyl)(phenyl)methyl)(methyl)carbamate (4c):** The reaction was performed following General Procedure B with *N*-Boc benzylmethylamine (**1a**) (24.3 mg, 0.11 mmol, 1 equiv), $LiN(SiMe_3)_2$ (66.9 mg, 0.4 mmol, 4 equiv) and aryl electrophile (0.1 mmol, 1.1 equiv) in 1 mL of THF (0.1 M). The crude reaction mixture was filtered through a short pad of silica to afford the product (>95% ^{1}H NMR yield with internal standard CH_2Br_2). The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4c** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 4H), 7.28 (d, J = 6.7 Hz, 1H), 7.20 (d, J = 7.5 Hz, 2H), 7.10 (d, J = 8.2 Hz, 2H), 6.57 (s, 1H), 2.67 (s, 3H), 1.46 (s, 9H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 150.0, 139.9, 136.4, 128.4, 128.3, 128.2, 127.0, 125.1, 79.7, 34.4, 31.3, 30.8, 28.4 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR (neat) 3029, 2965, 2869, 1693, 1603, 1490, 1389, 1257, 1172, 1142, 1018 cm^{-1}; HRMS *m/z* 376.2249 [$(M+Na)^+$; calcd for $C_{23}H_{31}NO_2Na^+$: 376.2252].

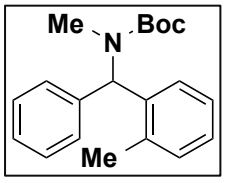
With 4-*t*bu-bromobenzene: Mass & Yield of **4c** = 32.0 mg, 90%.

With 4-*t*bu-phenyl triflate: Mass & Yield of **4c** = 32.2 mg, 91%.



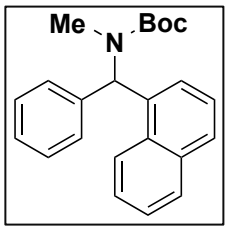
***tert*-Butyl-methyl(phenyl(*m*-tolyl)methyl)carbamate (4d):** The reaction was performed following General Procedure B with *N*-Boc benzylmethylamine (**1a**) (24.3 mg,

0.11 mmol, 1.1 equiv), $LiN(SiMe_3)_2$ (66.9 mg, 0.4 mmol, 4 equiv) and 3-bromotoluene (12.1 μL, 0.1 mmol, 1 equiv) in 1 mL of THF (0.1 M). The crude reaction mixture was filtered through a short pad of silica to afford the product (>95% ^{1}H NMR yield with internal standard CH_2Br_2). The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4d** as a colorless oil (26.8 mg, 86% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.15 (m, 6H), 7.15 – 7.08 (m, 1H), 7.06 – 6.95 (m, 2H), 6.57 (s, 1H), 2.69 (s, 3H), 2.34 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 140.2, 140.0, 138.2, 129.6, 128.9, 128.6, 128.4, 128.2, 127.4, 126.0, 80.1, 31.3, 28.7, 21.8 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR (neat) 3028, 2975, 2928, 1693, 1607, 1479, 1388, 1257, 1179, 1140 cm^{-1}; HRMS *m/z* 334.1783 [$(M+Na)^+$; calcd for $C_{20}H_{25}NO_2Na^+$: 334.1783].



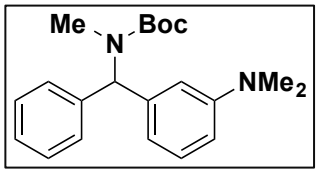
***tert*-Butyl-methyl(phenyl(*o*-tolyl)methyl)carbamate (4e):** The reaction was performed following General Procedure B with *N*-Boc benzylmethylamine (**1a**) (100 mg, 0.45 mmol, 1.5 equiv), $LiN(SiMe_3)_2$ (301 mg, 1.8 mmol, 6 equiv) and 2-bromotoluene (35.9 μL, 0.3 mmol, 1 equiv) in 1 mL of THF (0.3 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4e** as a colorless oil (46.5 mg, 50% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.29 (dd, J = 22.1, 7.5 Hz, 1H), 7.29 – 7.20 (m, 2H),

7.21 – 7.16 (m, 3H), 6.93 (d, J = 7.6 Hz, 1H), 6.53 (s, 1H), 2.65 (s, 3H), 2.24 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 140.1, 138.7, 137.1, 130.5, 128.4, 128.3, 127.9, 127.3, 126.9, 125.6, 79.5, 31.6, 28.3, 18.9 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR (neat) 3064, 3028, 2975, 2930, 1694, 1603, 1480, 1452, 1390, 1173, 1143 cm^{-1}; HRMS *m/z* 334.1786 [$(M+Na)^+$; calcd for $C_{20}H_{25}NO_2Na^+$: 334.1783].

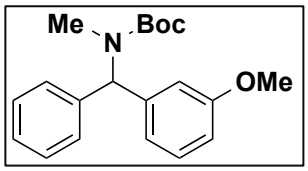


***tert*-Butyl-methyl(naphthalen-1-yl(phenyl)methyl)carbamate (4f):** The reaction was performed following General Procedure B with *N*-Boc benzylmethylamine (**1a**) (48.6 mg, 0.22 mmol, 1.1 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.8 mmol, 4 equiv) and 1-bromonaphthalene (27.9 μL, 0.2 mmol, 1 equiv) in 1 mL of THF (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4f** as a colorless oil (54.2 mg, 78% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.91 – 7.84 (m, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.55 – 7.46 (m, 2H), 7.42 – 7.26 (m, 4H), 7.20 (d, J = 7.6 Hz, 2H), 7.09 (d, J = 7.2 Hz, 1H), 2.63 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 140.5, 136.3, 133.7, 132.1, 128.7, 128.4, 128.4, 127.9, 127.1, 127.1, 127.0, 126.5, 125.7, 124.9, 79.9, 31.4, 28.3 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR

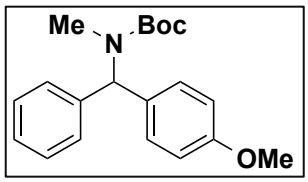
(neat) 3051, 3004, 2975, 2837, 1689, 1611, 1511, 1389, 1250, 1177, 1143, 1036 cm^{-1}; HRMS *m/z* 348.164 [$(M+H)^+$; calcd for $C_{23}H_{26}NO_2^+$: 348.1964].



***tert*-Butyl-((3-(dimethylamino)phenyl)(phenyl)methyl)(methyl)carbamate (4g):** The reaction was performed following General Procedure B with *N*-Boc benzylmethylamine (**1a**) (24.3 mg, 0.11 mmol, 1 equiv), $LiN(SiMe_3)_2$ (66.9 mg, 0.4 mmol, 4 equiv) and 3-bromo-*N*,*N*-dimethylaniline (14 μL, 0.1 mmol, 1 equiv) in 1 mL of THF (0.1 M). The crude reaction mixture was filtered through a short pad of silica to afford the product (>95% ^{1}H NMR yield with internal standard CH_2Br_2). The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4g** as a colorless oil (31.6 mg, 93% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 2H), 7.29 – 7.24 (m, 2H), 7.24 – 7.15 (m, 3H), 6.66 (dd, *J* = 8.2, 2.7 Hz, 1H), 6.57 (s, 1H), 6.51 (d, *J* = 7.5 Hz, 1H), 2.90 (s, 6H), 2.70 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6, 151.0, 140.9, 140.5, 129.3, 128.9, 128.6, 127.4, 117.5, 113.6, 111.9, 80.1, 41.1, 31.5, 28.9 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR (neat) 3028, 2973, 2928, 1692, 1603, 1497, 1388, 1256, 1178, 1141 cm^{-1}; HRMS *m/z* 341.2225 [$(M+H)^+$; calcd for $C_{21}H_{29}N_2O_2^+$: 341.2229].



***tert*-Butyl-((3-methoxyphenyl)(phenyl)methyl)(methyl)carbamate (4h):** The reaction was performed following General Procedure B with *N*-Boc benzylmethylamine (**1a**) (48.6 mg, 0.22 mmol, 1.1 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.8 mmol, 4 equiv) and 3-anisole bromide (25.4 μL, 0.2 mmol, 1 equiv) in 1 mL of THF (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4h** as a colorless oil (41.0 mg, 64% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, J = 7.6 Hz, 2H), 7.30 – 7.22 (m, 2H), 7.19 (d, J = 7.3 Hz, 2H), 6.83 (dd, J = 8.2, 2.4 Hz, 1H), 6.79 – 6.75 (m, 1H), 6.75 – 6.72 (m, 1H), 6.56 (s, 1H), 3.77 (s, 3H), 2.68 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 156.1, 141.4, 139.6, 129.2, 128.6, 128.2, 127.2, 120.9, 114.5, 112.3, 79.9, 55.1, 31.0, 28.4 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR (neat) 3020, 2973, 2930, 1692, 1600, 1490, 1389, 1260, 1143, 1046 cm^{-1}; HRMS *m/z* 350.1727 [$(M+Na)^+$; calcd for $C_{20}H_{25}NO_3Na^+$: 350.1732].

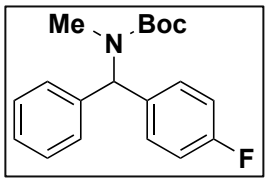


***tert*-Butyl-((4-methoxyphenyl)(phenyl)methyl)(methyl)carbamate (4i):** The reaction was performed following General Procedure B with *N*-Boc benzylmethylamine (**1a**) (48.6 mg, 0.22 mmol, 1.1 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.8 mmol, 4 equiv) and aryl

halide (0.2 mmol, 1 equiv) in 1 mL of THF (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4i** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 2H), 7.30 – 7.26 (m, 1H), 7.21 – 7.16 (m, 2H), 7.10 (d, J = 8.6 Hz, 2H), 6.90 – 6.79 (m, 2H), 6.53 (s, 1H), 3.81 (s, 3H), 2.66 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 156.2, 140.2, 131.9, 130.0, 128.3, 128.3, 127.1, 113.8, 79.9, 55.3, 30.9, 28.5 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR (neat) 3061, 3030, 3004, 2975, 2932, 2837, 1690, 1611, 1512, 1388, 1250, 1172, 1142, 1034 cm^{-1}; HRMS *m/z* 350.1717 [(M+Na)$^{+}$; calcd for $C_{20}H_{25}NO_3Na^{+}$: 350.1732].

With 4-bromoanisole: Mass & Yield of **4i**= 57.0 mg, 87%.

With 4-chloroanisole: Mass & Yield of **4i** = 55.6 mg, 85%.

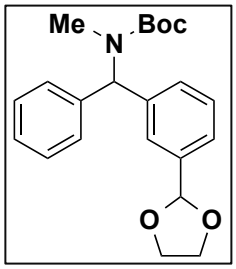


***tert*-Butyl-((4-fluorophenyl)(phenyl)methyl)(methyl)carbamate (4j):** The reaction was performed following General Procedure B with *N*-Boc benzylmethylamine (**1a**) (48.6 mg, 0.22 mmol, 1 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.8 mmol, 4 equiv) and aryl halide (0.2 mmol, 1 equiv) in 1 mL of THF (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4j** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 2H), 7.31 – 7.26 (m, 1H), 7.20 – 7.12 (m, 4H), 7.07 – 6.99 (m,

2H), 6.56 (s, 1H), 2.66 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9 (d, J = 246.1 Hz), 156.0, 139.5 , 135.5 (d, J = 3.3 Hz), 130.1 (d, J = 8.1 Hz), 128.4 , 128.3 , 127.3 , 115.1 (d, J = 21.4 Hz), 80.0, 30.8 , 28.4 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed).

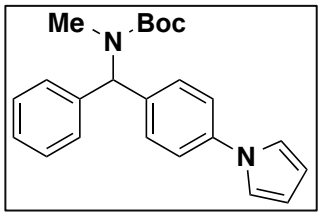
With 1-bromo-4-fluorobenzene: Mass & Yield of **4j** = 44.2 mg, 70%.

With 1-chloro-4-fluorobenzene: Mass & Yield of **4j** = 37.8 mg, 60%.

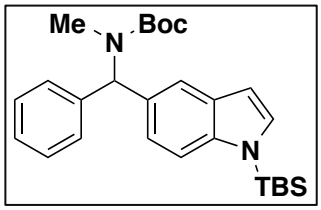


***tert*-Butyl-((3-(1,3-dioxolan-2-yl)phenyl)(phenyl)methyl)(methyl)carbamate (4k):** The reaction was performed following General Procedure B with *N*-Boc benzylmethylamine (**1a**) (48.6 mg, 0.22 mmol, 1 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.8 mmol, 4 equiv) and 2-(3-bromophenyl)-1,3-dioxolane (30.3 μL, 0.2 mmol, 1 equiv) in 1 mL of THF (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4k** as a colorless oil (50.2 mg, 68% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 7.6 Hz, 1H), 7.39 – 7.28 (m, 6H), 7.18 (m, 2H), 6.60 (s, 1H), 5.79 (s, 1H), 4.14 – 4.07 (m, 2H), 4.06 – 3.99 (m, 2H), 2.68 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 139.9, 139.5, 138.0, 129.4, 128.5, 128.4, 128.3, 127.2, 126.8, 125.3, 103.6, 79.9, 65.2, 31.0, 28.4 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR

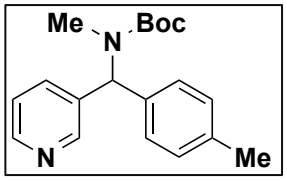
(neat) 2975, 2888, 1691, 1600, 1478, 1388, 1256, 1141, 1080 cm^{-1}; HRMS *m/z* 392.1838 [$(M+Na)^+$; calcd for $C_{22}H_{27}NO_4Na^+$: 392.1838].



***tert*-Butyl-((4-(1*H*-pyrrol-1-yl)phenyl)(phenyl)methyl)(methyl)carbamate (4l):** The reaction was performed following General Procedure B with *N*-Boc benzylmethylamine (**1a**) (48.6 mg, 0.22 mmol, 1.1 equiv), $LiN(SiMe_3)_2$ (200.8 mg, 1.2 mmol, 6 equiv) and 1-(4-chlorophenyl)-1*H*-pyrrole (35.6 μL, 0.2 mmol, 1 equiv) in 1 mL of THF (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product (>99% ^1H NMR yield with internal standard CH_2Br_2). The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4l** as a colorless oil (68.9 mg, 95% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 4H), 7.34 – 7.29 (m, 1H), 7.27 – 7.18 (m, 4H), 7.09 (t, *J* = 2.2 Hz, 2H), 6.61 (s, 1H), 6.35 (t, *J* = 2.2 Hz, 2H), 2.70 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 139.7, 139.4, 137.1, 129.7, 128.5, 128.4, 128.4, 127.3, 127.1, 120.2, 119.2, 110.4, 80.0, 30.9, 28.4 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR (neat) 3020, 2975, 2929, 1691, 1612, 1521, 1480, 1390, 1330, 1256, 1171, 1142, 1070cm^{-1}; HRMS *m/z* 363.2072 [$(M+H)^+$; calcd for $C_{23}H_{27}N_2O_2^+$: 363.2073].

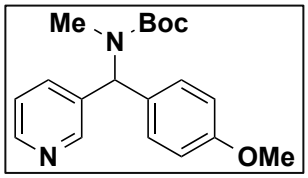


***tert*-Butyl-((1-(*tert*-butyldimethylsilyl)-1*H*-indol-5-yl)(phenyl)methyl)(methyl) carbamate (4m):** The reaction was performed following General Procedure B with *N*-Boc benzylmethylamine (**1a**) (48.6 mg, 0.21 mmol, 1.1 equiv), $LiN(SiMe_3)_2$ (234.0 mg, 1.4 mmol, 7 equiv) and 5-bromo-1-(*tert*-butyldimethylsilyl)-1*H*-indole (62.1 mg, 0.2 mmol, 1 equiv) in 1 mL of THF (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4m** as a colorless oil (35.0 mg, 50% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J = 8.6 Hz, 1H), 7.41 – 7.37 (m, 1H), 7.37 – 7.31 (m, 2H), 7.31 – 7.22 (m, 3H), 7.18 (d, J = 3.1 Hz, 1H), 6.99 (dd, J = 8.7, 2.0 Hz, 1H), 6.68 (s, 1H), 6.55 (dd, J = 3.1, 0.9 Hz, 1H), 2.70 (s, 3H), 1.46 (s, 9H), 0.94 (s, 9H), 0.60 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 140.8, 140.2, 131.4, 131.2, 131.1, 128.5, 128.4, 128.2, 127.2, 126.8, 122.9, 121.0, 113.6, 104.9, 79.7, 31.0, 28.5, 26.3, 19.5, -4.0 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR (neat) 3028, 2957, 2930, 2859, 1692, 16004, 1490, 1470, 1389, 1177, 1146 cm^{-1}; HRMS *m/z* 473.2611 [$(M+Na)^+$; calcd for $C_{27}H_{38}N_2O_2NaSi^+$: 473.2600].



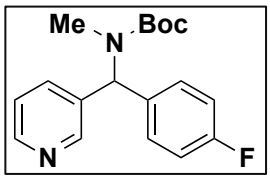
***tert*-Butyl-methyl(pyridin-3-yl(*p*-tolyl)methyl)carbamate (4n):** The reaction was

performed following General Procedure B with *N*-Boc-(3-pyridine-benzylmethyl)amine (**1d**) (24.5 mg, 0.11 mmol, 1.1 equiv), $LiN(SiMe_3)_2$ (66.9 mg, 0.4 mmol, 4 equiv) and bromotoluene (12.3 μL, 0.1 mmol, 1 equiv) in 1 mL of THF (0.1 M). The crude reaction mixture was filtered through a short pad of silica to afford the product (>99% ^{1}H NMR yield with internal standard CH_2Br_2). The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4n** as a colorless oil (30.0 mg, 98% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, J = 4.3 Hz, 1H), 8.50 (d, J = 1.2 Hz, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.26 (dd, J = 7.6, 5.0 Hz, 1H), 7.16 (d, J = 7.9 Hz, 2H), 7.05 (d, J = 7.9 Hz, 2H), 6.58 (s, 1H), 2.68 (s, 3H), 2.36 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 150.2, 148.8, 137.7, 136.1, 135.9, 135.7, 129.5, 128.8, 123.4, 80.5, 31.1, 28.6, 21.3 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR (neat) 3027, 3004, 2975, 2974, 1692, 1576, 1478, 1388, 1313, 1257, 1169, 1144, 1024 cm^{-1}; HRMS *m/z* 313.1920 [$(M+H)^+$; calcd for $C_{19}H_{25}N_2O_2^+$: 313.1916].



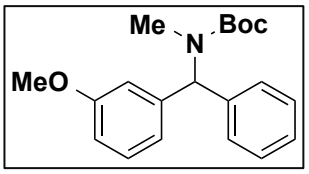
***tert*-Butyl-((4-methoxyphenyl)(pyridin-3-yl)methyl)(methyl)carbamate (4o):** The reaction was performed following General Procedure B with *N*-Boc-(3-pyridine-benzylmethyl)amine (**1d**) (24.5 mg, 0.11 mmol, 1.1 equiv), $LiN(SiMe_3)_2$ (83.7 mg, 0.5 mmol, 5 equiv) and 4-bromoanisole (12.5 μL, 0.1 mmol, 1 equiv) in 1 mL of THF (0.1 M). The crude reaction mixture was filtered through a short pad of silica to afford the

product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4o** as a colorless oil (29.9 mg, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 – 8.40 (m, 2H), 7.51 (dt, *J* = 7.7, 2.1 Hz, 1H), 7.32 – 7.25 (m, 1H), 7.09 (dd, *J* = 10.3, 3.8 Hz, 2H), 6.89 (td, *J* = 6.5, 5.7, 2.1 Hz, 2H), 6.59 (s, 1H), 3.82 (s, 3H), 2.68 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 155.9, 149.8, 148.5, 135.7, 130.5, 129.9, 123.2, 114.0, 80.3, 55.3, 30.8, 28.4 (one aromatic carbon is overlapping; (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR (neat) 3020, 3000, 2974, 2932, 1690, 1611, 1513, 1388, 1251, 1171, 1143, 1028 cm^{-1}; HRMS *m/z* 329.1870 [$(M+H)^+$; calcd for $C_{19}H_{25}N_2O_3^+$: 329.1865].

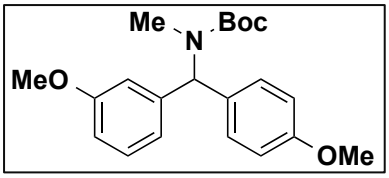


***tert*-Butyl-((4-fluorophenyl)(pyridin-3-yl)methyl)(methyl)carbamate (4p):** The reaction was performed following General Procedure B with *N*-Boc-(3-pyridine-benzylmethyl)amine (**1d)** (49.1 mg, 0.22 mmol, 1.1 equiv), $LiN(SiMe_3)_2$ (167.3 mg, 1.0 mmol, 5 equiv) and 1-bromo-4-fluorobenzene (21.2 μL, 0.2 mmol, 1 equiv) in 1 mL of THF (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4p** as a colorless oil (45.6 mg, 72% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.3 Hz, 1H), 8.49 (s, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.29 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.17 – 7.14 (m, 2H), 7.10 – 7.02 (m, 2H), 6.61 (s, 1H), 2.68 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5 (d, *J* = 246Hz), 156.1, 150.2, 149.1, 136.2, 135.4,

134.5, 130.5 (d, J = 8Hz), 123.5, 115.9 (d, J = 21Hz), 80.8, 31.1, 28.7 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR (neat) 3005, 2977, 2930, 1691, 1605, 1509, 1388, 1317, 1226, 1161, 1145, 1025 cm^{-1}; HRMS *m/z* 317.1665 [$(M+H)^+$; calcd for $C_{18}H_{22}N_2O_2F^+$: 317.1665].

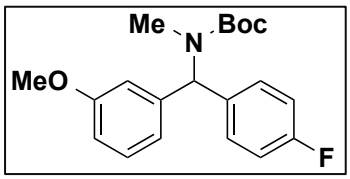


***tert*-Butyl-((3-methoxyphenyl)(phenyl)methyl)(methyl)carbamate (4h):** The reaction was performed following General Procedure B with *N*-Boc-(3-MeO-benzylmethyl)amine (**1c)** (55.3 mg, 0.22 mmol, 1.1 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.8 mmol, 4 equiv) and bromobenzene (21.0 μL, 0.2 mmol, 1 equiv) in 1 mL of THF (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product (>99% ^{1}H NMR yield with internal standard CH_2Br_2). The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4h** as a colorless oil (58.9 mg, 90% yield). See above for the spectral data on page 23.



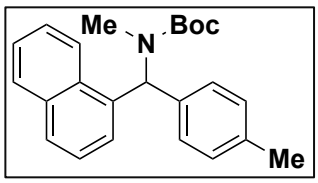
***tert*-Butyl-((3-methoxyphenyl)(4-methoxyphenyl)methyl)(methyl)carbamate (4q):** The reaction was performed following General Procedure B with *N*-Boc-(3-MeO-benzylmethyl)amine (**1c)** (55.3 mg, 0.22 mmol, 1.1 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.8 mmol, 4 equiv) and 4-bromoanisole (25.1 μL, 0.2 mmol, 1 equiv) in 1 mL of THF (0.2

M). The crude reaction mixture was filtered through a short pad of silica to afford the product (>99% ^{1}H NMR yield with internal standard CH_2Br_2). The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4q** as a colorless oil (62.2 mg, 87% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.81 (dd, *J* = 8.1, 2.3 Hz, 1H), 6.76 (dd, *J* = 7.6, 0.7 Hz, 1H), 6.74 – 6.70 (m, 1H), 6.50 (s, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 2.66 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 159.1, 156.4, 142.1, 132.0, 130.3, 129.5, 121.0, 114.5, 114.0, 112.5, 80.1, 55.5, 55.5, 31.2, 28.7 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR (neat) cm^{-1}; HRMS *m/z* 380.1830 [$(M+Na)^+$; calcd for $C_{21}H_{27}NO_4Na^+$: 380.1838].



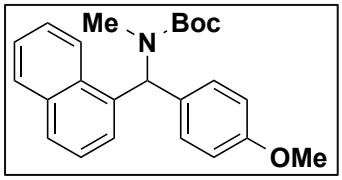
***tert*-Butyl-((4-fluorophenyl)(3-methoxyphenyl)methyl)(methyl)carbamate (4r):** The reaction was performed following General Procedure B with *N*-Boc-(3-MeO-benzylmethyl)amine (**1c)** (55.3 mg, 0.22 mmol, 1 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.8 mmol, 4 equiv) and 1-chloro-4-fluorobenzene (21.0 μL, 0.2 mmol, 1 equiv) in 1 mL of THF (0.1 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4r** as a colorless oil (39.4 mg, 57% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 1H), 7.20 – 7.13 (m, 2H), 7.06 – 6.99 (m, 2H), 6.83 (dd, *J* = 8.4, 2.6 Hz, 1H),

6.75 (dq, J = 7.7, 0.9 Hz, 1H), 6.72 – 6.68 (m, 1H), 6.53 (s, 1H), 3.78 (s, 3H), 2.66 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0 (d, J = 246.0 Hz), 159.7 , 156.1 , 141.3 , 135.5 (d, J = 3.3 Hz), 130.2 (d, J = 7.9 Hz), 129.4, 120.9, 115.2 (d, J = 21.4 Hz), 114.5, 112.4 , 80.1, 55.2, 31.0, 28.4 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR (neat) 3020, 2974, 2932, 1694, 1602, 1508, 1455, 1391, 1260, 1144, 1048 cm^{-1}; HRMS *m/z* 368.1619 [$(M+Na)^+$; calcd for $C_{20}H_{24}NO_3FNa^+$: 368.1626].

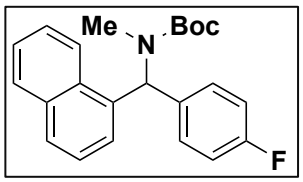


***tert*-Butyl-methyl(naphthalen-2-yl(*p*-tolyl)methyl)carbamate (4s):** The reaction was performed following General Procedure B with *N*-Boc-(1-naphthalenebenzylmethyl)amine (**1g)** (29.9 mg, 0.11 mmol, 1.1 equiv), $LiN(SiMe_3)_2$ (117.1 mg, 0.7 mmol, 7 equiv) and 4-bromotoluene (12.3 mL, 0.1 mmol, 1 equiv) in 1 mL of THF (0.1 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4s** as a colorless oil (25.3 mg, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.93 – 7.89 (m, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.41 (t, J = 7.7 Hz, 1H), 7.22 – 7.08 (m, 6H), 2.67 (s, 3H), 2.40 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 137.3, 136.6, 136.5, 133.7, 132.0, 129.1, 128.6, 128.2, 127.9, 126.8, 126.4, 125.7, 124.9, 123.7, 79.5, 30.9, 28.3, 21.1 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR (neat) 3050, 3006, 2975, 2928, 1692, 1600, 1512,

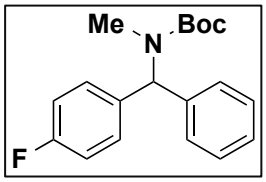
1389, 1366, 1257, 1143 cm^{-1}; HRMS *m/z* 384.1932 [$(M+Na)^+$; calcd for $C_{24}H_{27}NO_2Na^+$: 384.1939].



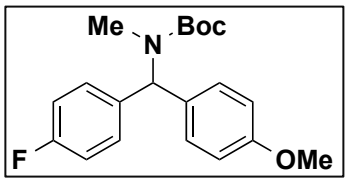
***tert*-Butyl-((4-methoxyphenyl)(naphthalen-2-yl)methyl)(methyl)carbamate (4t):** The reaction was performed following General Procedure B with *N*-Boc-(1-naphthalenebenzylmethyl)amine (**1g)** (54.3 mg, 0.22 mmol, 1.1 equiv), $LiN(SiMe_3)_2$ (167.3 mg, 1.0 mmol, 5 equiv) and 4-bromoanisole (25.1 μL, 0.2 mmol, 1 equiv) in 1 mL of THF (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4t** as a colorless oil (43.0 mg, 57% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.93 – 7.82 (m, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.61 – 7.43 (m, 2H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.20 – 6.99 (m, 4H), 7.01 – 6.67 (m, 2H), 3.80 (s, 3H), 2.63 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 156.0, 136.7, 133.8, 132.5, 132.0, 129.3, 128.7, 128.3, 126.6, 126.4, 125.7, 125.0, 124.0, 113.9, 79.9, 55.3, 31.5, 28.4 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR (neat) cm^{-1}; HRMS *m/z* 378.2077 [$(M+H)^+$; calcd for $C_{24}H_{28}NO_3^+$: 378.2069].



***tert*-Butyl-((4-fluorophenyl)(naphthalen-2-yl)methyl)(methyl)carbamate (4u):** The reaction was performed following General Procedure B with *N*-Boc-(1-naphthalenebenzylmethyl)amine (**1g)** (27.1 mg, 0.1 mmol, 2 equiv), $LiN(SiMe_3)_2$ (50.2 mg, 0.3 mmol, 6 equiv), $Pd(OAc)_2$ (10 mol%), NiXantphos (20 mol%), and 1-bromo 4-fluorobenzene (5.5 μL, 0.05 mmol, 1 equiv) in 1 mL of THF (0.05 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4u** as a colorless oil (14.2 mg, 78% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.92 – 7.86 (m, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.30 (s, 1H), 7.16 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.05 (q, *J* = 8.7, 7.9 Hz, 3H), 2.61 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9 (d, *J* = 246.9 Hz), 155.9, 136.12, 133.8, 132.0, 129.5 (d, *J* = 7.8 Hz), 128.8, 128.6, 128.4, 127.0, 126.6, 125.9, 125.0, 123.9, 115.4 (d, *J* = 20.9 Hz), 80.2, 31.4, 28.4 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR (neat) 3020, 2974, 2930, 1691, 1604, 1509, 1389, 1256, 1225, 1159, 1142, 1015 cm^{-1}; HRMS *m/z* 388.1601 [$(M+Na)^+$; calcd for $C_{23}H_{24}FNO_2Na^+$: 388.1683].

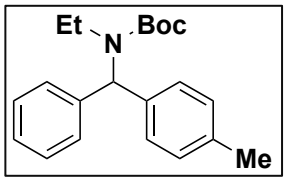


***tert*-Butyl-((4-fluorophenyl)(phenyl)methyl)(methyl)carbamate (4j):** The reaction was performed following General Procedure B with *N*-Boc-(4-fluoro-benzylmethyl)amine (**1g)** (48.0 mg, 0.22 mmol, 1 equiv), $LiN(SiMe_3)_2$ (133.9 mg, 0.8 mmol, 4 equiv), and bromobenzene (21.0 μL, 0.2 mmol, 1 equiv) in 1 mL of THF (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4j** as a colorless oil (47.9 mg, 76% yield). See above for the spectral data on page 10.

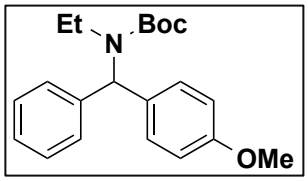


***tert*-Butyl-((4-fluorophenyl)(4-methoxyphenyl)methyl)(methyl)carbamate (4v):** The reaction was performed following General Procedure A with *N*-Boc-(4-fluoro-benzylmethyl)amine (48.0 mg, 0.22 mmol, 1 equiv), $LiN(SiMe_3)_2$ (167.3 mg, 1.0 mmol, 5 equiv), and 4-bromoanisole (25.1 μL, 0.2 mmol, 1 equiv) in 1 mL of THF (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4v** as a colorless oil (50.4 mg, 73% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (dd, J = 8.5, 5.4 Hz, 2H), 7.09

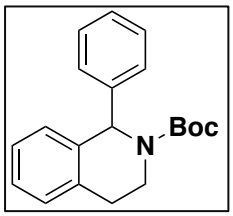
(d, J = 8.4 Hz, 2H), 7.02 (t, J = 8.6 Hz, 2H), 6.91 – 6.84 (m, 2H), 6.51 (s, 1H), 3.81 (s, 3H), 2.65 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9 (d, J = 243.8 Hz), 158.9, 156.1, 135.9 (d, J = 8.0 Hz), 131.6, 129.9, 129.8, 115.2 (d, J = 21.3 Hz), 113.8, 80.0, 55.3, 30.8, 28.5 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR (neat) 3040, 2975, 2933, 1693, 1605, 1509, 1480, 1392, 1367, 1249, 1147, 1034 cm^{-1}; HRMS *m/z* 368.1638 [(M+Na)$^+$; calcd for $C_{20}H_{24}NO_3FNa^+$: 368.1637].



***tert*-Butyl-ethyl(phenyl(*p*-tolyl)methyl)carbamate (4w):** The reaction was performed following General Procedure B with *N*-Boc benzylethylamine (**1b)** (56.5 mg, 0.24 mmol, 1.2 equiv), $LiN(SiMe_3)_2$ (335.0 mg, 2 mmol, 10 equiv) and 4-bromotoluene (25.1 μL, 0.2 mmol, 1 equiv) in 1 mL of THF (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4w** as a colorless oil (48.8 mg, 75% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 7.25 (tt, J = 7.0, 1.5 Hz, 1H), 7.19 (dd, J = 7.1, 1.9 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.1 Hz, 2H), 6.49 (s, 1H), 3.25 (ddt, J = 16.2, 14.1, 7.1 Hz, 2H), 2.34 (s, 3H), 1.43 (s, 9H), 0.67 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 141.0, 137.6, 137.0, 129.2, 129.0, 128.8, 128.4, 127.2, 79.8, 41.5, 40.3, 28.7, 21.3, 14.5 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR (neat) 3062, 3028, 2975, 2932, 1692, 1603, 1495, 1454, 1407, 1365, 1254, 1172, 1142 cm^{-1}; HRMS *m/z* 348.1934 [(M+Na)$^+$; calcd for $C_{21}H_{27}NO_2Na^+$: 348.1939].

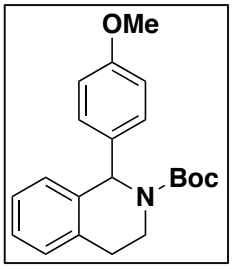


***tert*-Butyl-ethyl((4-methoxyphenyl)(phenyl)methyl)carbamate (4x):** The reaction was performed following General Procedure B with *N*-Boc benzylethylamine (**1b)** (83.6 mg, 0.33 mmol, 1 equiv), $LiN(SiMe_3)_2$ (402 mg, 2.4 mmol, 8 equiv) and 4-bromoanisole (37.5 μL, 0.3 mmol, 1 equiv) in 1.5 mL of THF (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4x** as a colorless oil (61.5 mg, 60% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 2H), 7.28 – 7.24 (m, 1H), 7.21 – 7.16 (m, 2H), 7.15 – 7.10 (m, 2H), 6.89 – 6.83 (m, 2H), 6.49 (s, 1H), 3.81 (s, 3H), 3.30 (dq, *J* = 13.9, 6.9 Hz, 1H), 3.19 (dq, *J* = 13.9, 6.9 Hz, 1H), 1.44 (s, 9H), 0.67 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 140.8, 132.5, 131.7, 130.1, 128.4, 128.2, 127.0, 113.6, 79.6, 55.3, 40.0, 28.5, 25.4, 14.3 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); HRMS *m/z* 364.1985 [$(M+Na)^+$; calcd for $C_{21}H_{27}NO_2Na^+$: 364.1883].



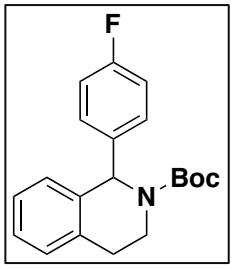
***tert*-Butyl-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (4aa):** The reaction was performed following General Procedure B with *N*-Boc-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**1aa**) (47.0 mg, 0.2 mmol, 1 equiv), $LiN(SiMe_3)_2$ (234.0 mg, 1.4

mmol, 7 equiv) and bromobenzene (31.5 μL, 0.3 mmol, 1.5 equiv) in 1 mL of THF (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4aa** as a colorless oil (50.2 mg, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$, rotomer) δ 7.34 – 7.12 (m, 8H), 7.11 – 6.97 (m, 1H), 6.26 (m, 1H, rotomers), 4.06 (s, 1H, rotomer), 3.21 (ddd, *J* = 13.2, 10.7, 4.4 Hz, 1H), 2.96 (s, 1H), 2.88 – 2.65 (m, 1H, rotomer), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 143.1, 135.7, 135.3, 128.9, 128.5, 128.3, 128.2, 127.2, 126.8, 126.0, 80.0, 57.5, 37.9, 28.5 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR (neat) 3062, 3030, 2974, 2930, 1693, 1601, 1493, 1417, 1392, 1250, 1171, 1120, 1094, 1031 cm^{-1}; HRMS *m/z* 332.1628 [$(M+Na)^+$; calcd for $C_{20}H_{23}NO_2Na^+$: 332.1626].



***tert*-Butyl-1-(4-methoxyphenyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (4ab):** The reaction was performed following General Procedure B with *N*-Boc-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**1aa**) (47.0 mg, 0.2 mmol, 1 equiv), $LiN(SiMe_3)_2$ (234.0 mg, 1.4 mmol, 7 equiv) and 4-bromoanisole (30.0 μL, 0.24 mmol, 1.2 equiv) in 1 mL of THF (0.2 M). The crude reaction mixture was filtered through a short pad of silica

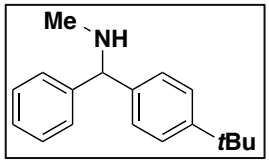
to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4ab** as a colorless oil (51.6 mg, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.09 (m, 5H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.83 – 6.74 (m, 2H), 6.30 (m, 1H, rotomer), 4.10 (m, 1H, rotomer), 3.77 (s, 3H), 3.16 (ddd, *J* = 13.2, 11.1, 4.2 Hz, 1H), 3.04 – 2.87 (m, 1H), 2.74 (d, *J* = 16.1 Hz, 1H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, rotomers) δ 158.7, 154.6, 135.9, 135.5, 135.2, 129.5, 128.9, 128.5, 126.7, 125.9, 113.5, 79.9, 57.1, 37.0, 55.2, 28.6 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR 3064, 3004, 2932, 2975, 2837, 1693, 1610, 1510, 1417, 1365, 1248, 1171, 1120, 1036 cm^{-1}; HRMS *m/z* 362.1732 [$(M+Na)^+$; calcd for $C_{21}H_{25}O_3NNa^+$: 362.1732].



***tert*-Butyl-1-(4-fluorophenyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (4ac):** The reaction was performed following General Procedure B with *N*-Boc-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**1aa**) (47.0 mg, 0.2 mmol, 1 equiv), $LiN(SiMe_3)_2$ (234.0 mg, 1.4 mmol, 7 equiv) and 1-bromo-4-fluorobenzene (31.5 μL, 0.3 mmol, 1.5 equiv) in 1 mL of THF (0.2 M). The crude reaction mixture was filtered through a short pad of silica to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product **4ac** as a colorless oil (42.6 mg, 65% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25

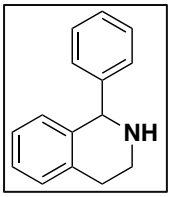
– 7.13 (m, 5H), 7.02 (d, J = 7.4 Hz, 1H), 6.95 (td, J = 9.1, 8.6, 2.4 Hz, 2H), 6.31 (m, 1H, rotomer), 4.05 (m, 1H, rotomer), 3.16 (ddd, J = 13.0, 10.7, 4.3 Hz, 1H), 3.03 – 2.92 (m, 1H), 2.75 (d, J = 16.4 Hz, 1H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0 (d, J = 246.1 Hz), 154.7, 139.0, 135.3 (d, J = 28.1 Hz), 129.9 (d, J = 7.9 Hz), 129.0, 128.5, 128.2, 127.0, 126.1, 114.9 (d, J = 21.6 Hz), 80.2, 57.7, 38.1, 28.5 (the quaternary C of the $CO_2C(CH_3)_3$ is not observed); IR 3064, 3006, 2975, 29 30, 1693, 1604, 1507, 1417, 1366, 1233, 1170, 1120, 1094 cm^{-1}; HRMS *m/z* 350.1532 [$(M+Na)^+$; calcd for $C_{20}H_{22}O_2FNa^+$: 350.1532].

Procedure and Characterization of 2^0 free Diarylmethylamines.



1-(4-(*tert*-Butyl)phenyl)-*N*-methyl-1-phenylmethanamine (5c): 10 M Hydrochloric acid (100 μL, 0.1 mmol) was added dropwise to a solution of *N*-Boc 1,2,3,4-tetrahydroisoquinoline **4ab** (11 mg, 0.03 mmol) in ethyl acetate (2 mL), and the mixture was stirred at room temperature. After 6 h of stirring, the organic layer was washed twice with 1 M NaOH solution (15 mL/wash), and the mixture was extracted twice with CH_2Cl_2 (20 ml/wash). The combined extracts were dried over sodium sulfate, filtered, and the solvent was removed under reduced pressure to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 40:60) to give the product **5c** (5.1 mg, 75% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 2H), 7.35 – 7.27 (m, 6H),

7.24 – 7.14 (m, 1H), 4.67 (s, 1H), 2.40 (s, 3H), 1.62 (s, 1H), 1.28 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8, 144.1, 141.0, 128.4, 127.3, 126.9, 126.8, 125.3, 69.3, 35.2, 34.4, 31.4; IR (neat) 3338, 3027, 2962, 2788, 1550, 1490, 1453, 1364, 1268, 1110, 1019 cm^{-1}; HRMS *m/z* 252.1741 [$(M-H)^+$; calcd for $C_{18}H_{22}N^+$: 252.1752].



1-Phenyl-1,2,3,4-tetrahydroisoquinoline (5aa): 10 M Hydrochloric acid (100 μL, 1.0 mmol) was added dropwise to a solution of *N*-Boc tetrahydroisoquinoline **1aa** (115 mg, 0.4 mmol) in ethyl acetate (3 mL), and the mixture was stirred at room temperature. After 6 h of stirring, the organic layer was washed twice with 1 M NaOH solution (15 mL/wash), and the mixture was extracted twice with CH_2Cl_2 (20 ml/wash). The combined extracts were dried over sodium sulfate, filtered, and the solvent was removed under reduced pressure to afford the product. The crude material was then purified by flash column chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 40:60) to give the product **5aa** (73.6 mg, 95% yield) as a colorless oil. The NMR spectral data match the previously published data. [33]

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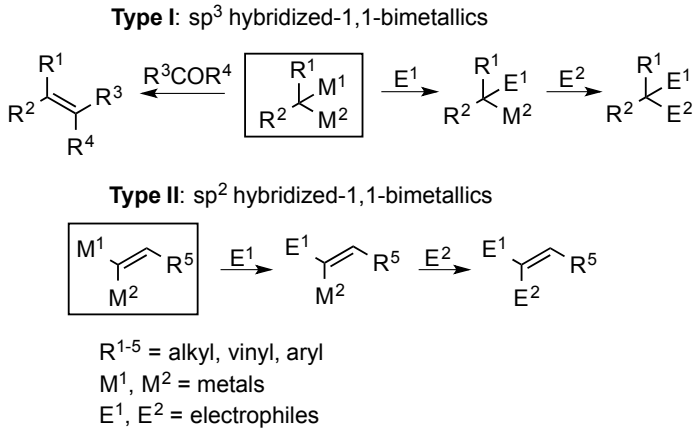
CHAPTER 3
Stereoselective Vinylation of Aryl *N*-(2-Pyridylsulfonyl) Aldimines with 1-Alkenyl-1,1- Heterobimetallic Reagents[iii][iv]

1. Introduction:

Highly stereoselective construction of C–C double bonds remains a challenge in organic synthesis.[1] In this regard, sp^3 and sp^2 hybridized heterobimetallic reagents of type I and II (Scheme 1) are potentially useful intermediates, because each metal-carbon bond can be chemoselectively exploited in C–C bond forming reactions.[2-6] Furthermore, these versatile heterobimetallic reagents can be employed in tandem reactions, minimizing isolation and purification of intermediates.[5] These attributes allow for rapid development of molecular complexity from simple building blocks.

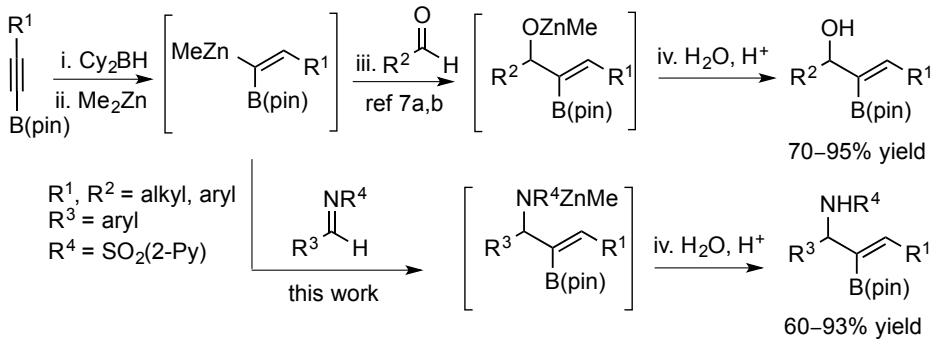


Scheme 1: 1,1-Heterobimetallics in Organic Synthesis.

[iii] [N. Hussain, M. M. Hussain, M. Ziauddin, P. Triyawatanyu, P. J. Walsh, "*Stereoselective Vinylation of Aryl N-(2-Pyridylsulfonyl) Aldimines with 1-Alkenyl-1,1-Heterobimetallic Reagents*," Org. Lett. **2011**, *33*, 6464-6467] – Reproduced by permission of The American Chemical Society.

[iv] This Project was initiated by Dr. Mahmud Hussain.

As part of our program in developing stereoselective C–C bond forming reactions, we have reported the generation of 1-alkenyl-1,1-heterobimetallic reagents based on boron and zinc from readily available, air-stable B(pin)-substituted alkynes (Scheme 2).[7a] Thus, regioselective hydroboration of B(pin)-alkynes generates the 1,1-bis (boro) intermediates.[7a, 8] Chemoselective transmetallation of the more reactive vinyl-BCy_2 bond generates 1-alkenyl-1,1- heterobimetallic reagents. The difference in reactivity between Zn–C vs. B–C bonds allows for selective reaction at the Zn–C bond with aldehydes to yield B(pin)-substituted allylic zinc alkoxide intermediates. The alkoxide intermediates were then employed in various tandem reactions to form an array of compounds such as B(pin)-substituted allylic alcohols, α-hydroxy ketones, trisubstituted (*E*)-allylic alcohols, B(pin)-substituted cyclopropyl alcohols and B(pin)-substituted allylic acetates.[7a-d]

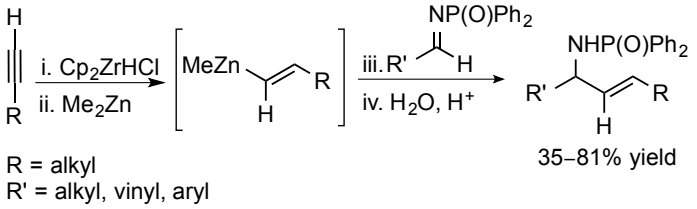


Scheme 2: Generation of 1-Alkenyl-1,1-heterobimetallics of Boron/Zinc and Additions to Electrophiles.

Herein, we report the addition of alkenyl-1,1- heterobimetallic reagents to *N*-(2-pyridylsulfonyl) aldimines to furnish B(pin)-substituted allylic amines (Scheme 2, lower part). The addition can be followed by oxidation of the B-C bond to provide α-

aminoketones or by Suzuki cross-coupling to provide densely functionalized trisubstituted (*E*)-allylic amines.

Allylic amines[9] are important pharmacophores that can exhibit significant biological properties. Examples include Acrivastine (Semprex),[10] Flunarizine, and several GABA uptake inhibitors.[12] As a result, additions to imines have attracted considerable attention. For example, Wipf and coworkers reported the addition of vinylzinc reagents to aldimines activated with a diphenylphosphonoyl moiety (Scheme 3).[13] Carretero[14a,b] and co-workers demonstrated that the reactivity of *N*-sulfonyl imines could be increased in the presence of an appropriately positioned heteroaryl group. Using this strategy, they developed the alkylation of aryl *N*-(2-pyridylsulfonyl) aldimines with organozinc halides.[14b] The Carretero and Toru groups both have utilized the *N*-pyridylsulfonyl as a novel stereocontrol element in enantioselective Mannich-type reactions with silyl enol ethers in the presence of chiral copper catalysts.[15] Various related nucleophilic reagents, such as dialkyl zinc,[5,16,17] alkynylzinc,[5,18] diethylaluminium cyanide and Danishefsky's diene[20] have also been investigated in imine addition reactions to yield the desired amines.



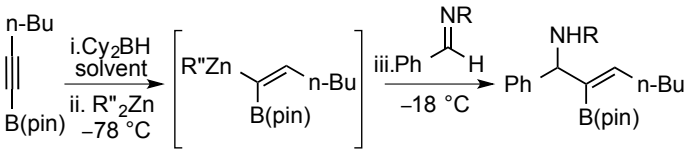
Scheme 3: Wipf's Vinylation of Aryl Diphenylphosphonoyl Imines via Vinylzinc Reagents.

2. Results and Discussions:

2.1. Optimization of the Addition of Alkenyl-1,1-heterobimetallics to *N*-Pyridyl Sulfonyl Imines.

Our first task in the addition of bimetallics to imines was to find a suitable imine activating group. The bimetallic reagent was generated and allowed to react with activated imines at -18 °C (Table 1). *N*-Tosylimines gave trace addition product with our alkenyl heterobimetallic reagents (entry 1). Rather, a significant amount of reduction product was isolated. The *N*-Boc imine behaved similarly, failing to furnish the desired amine (entry 2). When the activating group was changed to diphenylphosphinoyl, less than 30% of the allylic amine was isolated. Gratifyingly, the bimetallic addition to *N*-pyridyl sulfonyl imine occurred smoothly in 73% yield in toluene at -18 °C to furnish the desired product (entry 4). The addition was then optimized with the *N*-pyridyl sulfonyl imines. Switching the solvent from toluene to dicholoromethane improved the yields slightly (entry 4 vs. 7), while in THF, almost no product was formed (entry 5). Dimethylzinc performed better than diethylzinc (entry 7 vs. 9). Increasing the reaction temperature from –18 °C to -10 °C led to diminished yield (entry 6 vs. 7). With the optimized conditions in entry 7, the scope of the reaction was examined.

Table 1. Optimization of the Addition of Alkenyl-1,1-heterobimetallics to *N*-Pyridyl Sulfonyl Imines.[v]



entry	$R"_2Zn$	solvent	R	yield (%)[a]
1	Me_2Zn	toluene	SO_2Tol	trace
2	Me_2Zn	toluene	Boc	trace
3	Me_2Zn	toluene	$P(O)Ph_2$	<30
4	Me_2Zn	toluene	SO_2(2-Py)	73
5	Me_2Zn	THF	SO_2(2-Py)	trace
6	Me_2Zn	CH_2Cl_2	SO_2(2-Py)	68[b]
7	Me_2Zn	CH_2Cl_2	SO_2(2-Py)	80
8	Et_2Zn	toluene	SO_2(2-Py)	64
9	Et_2Zn	CH_2Cl_2	SO_2(2-Py)	65

[a] Isolated yields, [b] Reaction performed at –10 °C

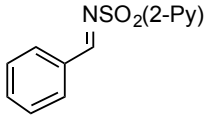
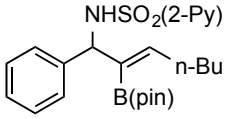
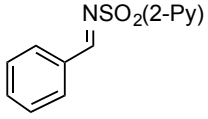
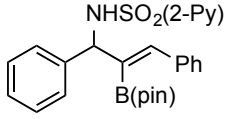
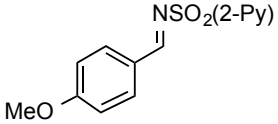
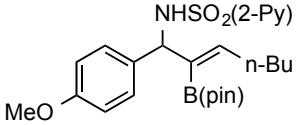
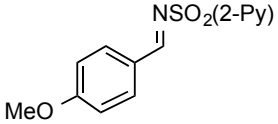
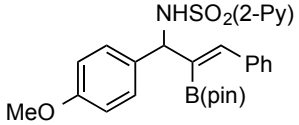
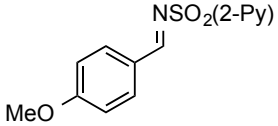
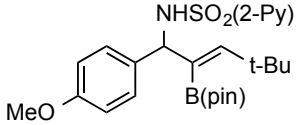
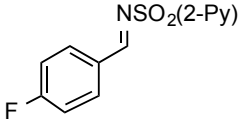
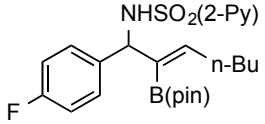
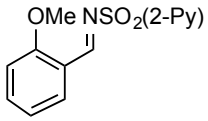
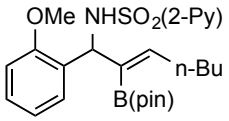
2.2. Substrate Scope of 2-B(pin)-substituted Allylic Amines: Addition of Alkenyl-1,1-heterobimetallics to *N*-Pyridyl Sulfonyl Imines.

Aryl aldimines with electron donating or electron withdrawing groups were good substrates, providing the B(pin) substituted allylic amines in 60–93% yield (Table 2). The air-stable B(pin)-substituted alkynes can contain aromatic or aliphatic substituents (R = aryl, alkyl). Even the bulky *tert*-butyl-substituted B(pin) alkyne underwent addition to generate the corresponding allylic amine in 60% yield (entry 5). Substitution at the *ortho* position of the aldimine resulted in slightly lower yield (entry 7 vs 3-5).

[v] Reactions 1, 2, 3 and 4 in Table 1 were performed by Dr. Mahmud Hussain, Plengchat Triyawatanyu and Muhammed Ziauddin.

Having established vinylation of aldimines with our heterobimetallics, we sought to examine tandem reactions involving the B–C bond. Two such reactions are B–C bond oxidation and Suzuki cross-coupling.

Table 2. Addition of Alkenyl-1,1-hetrobimetallics to *N*-Pyridyl Sulfonyl Imines.[vi]

entry	borane	imine	allylic amines		yield (%)[a]
1				**1a**	80
2				**1b**	68
3				**1c**	87
4				**1d**	93
5				**1e**	60
6				**1f**	70
7				**1g**	53

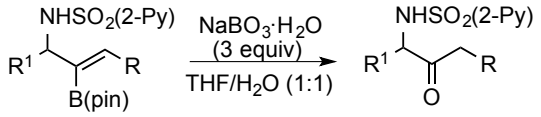
[a] Isolated yields

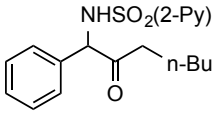
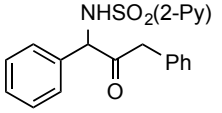
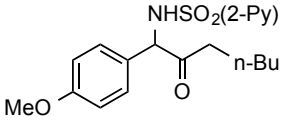
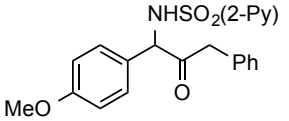
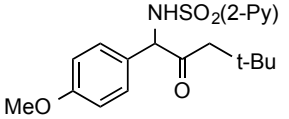
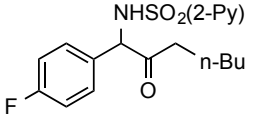
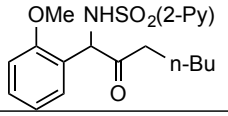
[vi] Muhammed Ziauddin also worked on evaluating the substrate scopes of Table 2.

2.3. Oxidation of 2-B(pin)-substituted Allylic Amines to α-Amino Ketones.

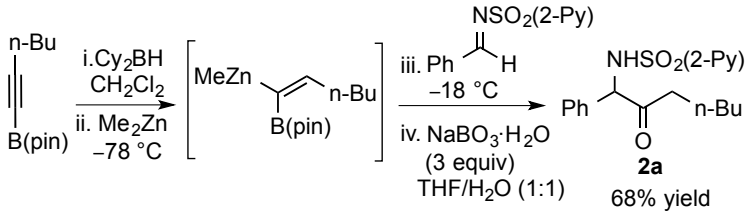
We envisioned that oxidation of the 2-B(pin)-substituted allylic amines would provide access to valuable *α*-amino ketones, which have important biological activity.[21] In the presence of $NaBO_3 \cdot H_2O$ in THF/H_2O (1:1) at rt, B(pin)-substituted allylic amines were smoothly oxidized to the corresponding *α*-amino ketones in 71–98% yield (Table 3). The addition/oxidation reaction can also be executed in a tandem fashion. Thus, after the completion of the bimetallic addition to the aldimine, the reaction mixture was subjected to $NaBO_3 \cdot H_2O$ to provide the *α*-amino ketone in 68% yield in one pot (Scheme 4).

Table 3: Oxidation of Allylic Amines to α-Amino Ketones.[vii]



entry	allylic amines	amino ketones		yield %[a]
1	**1a**		**2a**	80
2	**1b**		**2b**	75
3	**1c**		**2c**	96
4	**1d**		**2d**	98
5	**1e**		**2e**	87
6	**1f**		**2f**	71
7	**1g**		**2g**	87

[a] Isolated yields

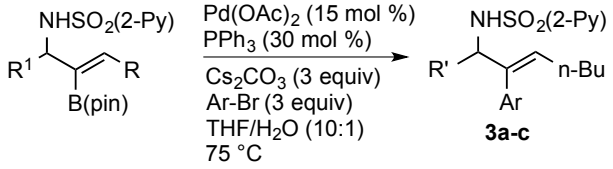


Scheme 4: Tandem Addition/B-C Bond Oxidation to Yield α-Amino Ketone **2a**.

[vii] Muhammed Ziauddin also worked on evaluating the substrate scopes of Table 3.

2.4. Suzuki Cross-coupling of 2-B(pin)-substituted Allylic Amines to Provide Tri-substituted (*E*)-Allylic Amines.

We next utilized the B–C bond in Suzuki cross-coupling reactions. In the presence of $Pd(OAc)_2$ (15 mol %), PPh_3 (30 mol %), Cs_2CO_3 (3 equiv) and aryl bromide (3 equiv) in THF/H_2O (10:1) at 75 °C, the B(pin)-substituted allylic amines smoothly underwent cross-coupling to furnish the 2-arylated trisubstituted (*E*)-allylic amines in 51–73% yield (Scheme 5). No (*Z*)-double bond isomers were observed in these reactions.

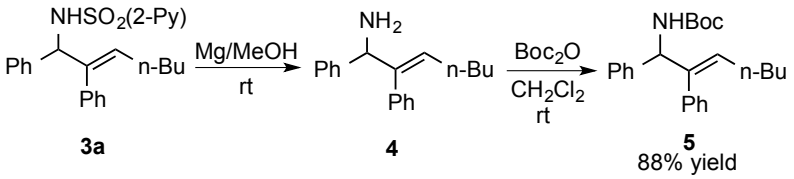


R' = Ph, Ar = Ph (**3a**), 73% yield
R' = 4-C_6H_4-OMe, Ar = 4-C_6H_4-OMe (**3b**), 70% yield
R' = 4-C_6H_4-F, Ar = Ph (**3c**), 51% yield

Scheme 5: Suzuki Cross-Coupling of Allylic Amines.

2.5. Removal of the 2-Pyridyl Sulfonyl Group Followed by Boc-protection.

Although the 2-pyridyl sulfonyl group is essential for the addition step, its removal is important for applications of the products. The 2-pyridyl sulfonyl group was readily cleaved on treatment of **1a** with magnesium in MeOH to liberate the free amine **4** (Scheme 6).[23,24] The free amine **4** was then transformed into its Boc-derivative **5** on treatment with Boc_2O at rt in 88% overall yield (Scheme 6).



Scheme 6: Removal of the 2-Pyridyl Sulfonyl Group followed by Boc-protection.

3. Conclusion:

In summary, the nucleophilic addition of 1-alkenyl-1,1-borozinc heterobimetallic reagents to aryl *N*-(2-pyridylsulfonyl) aldimines has been developed. This protocol provides a variety of B(pin)-substituted allylic amines in good yields. The addition step can be followed by a tandem oxidative cleavage of the B–C bond to furnish valuable α-amino ketones or by Suzuki cross-coupling to form 2-arylated trisubstituted (*E*)-allylic amines. It is noteworthy that 2-arylated trisubstituted (*E*)-allylic amines are not currently accessible via the Tsuji-Trost reaction, because 2-arylated allylic acetates are not good substrates for the allylic substitution reaction.[7d] Given that amino ketones and allylic amines are important pharmacophores, we anticipate that the methods described herein will be useful to the synthetic community.

Acknowledgements: I want to thank the co-authors of this heterobimetallics addition to aldimine project, Dr. Mahmud Hussain, Plengchat Triyawatanyu, and Muhammed Ziauddin. Dr. Hussain initiated this bimetallic addition reaction to aldimines. He, along with P. Triyawatanyu, synthesized the activated imines for the bimetallic addition to aldimines. I, along with M. Ziauddin, optimized the reaction

conditions of the bimetallic addition reaction to aldimies and evaluated the substrate scopes of the reaction.

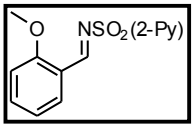
4. Experimental Section:

General Methods: All reactions were performed under a nitrogen atmosphere with oven-dried glassware. All manipulations involving dicyclohexylborane, diethylzinc, and dimethylzinc were carried out under an inert atmosphere in a Vacuum Atmospheres drybox with an attached MO-40 Dritrain or by using standard Schlenk or vacuum line techniques. Chemicals were obtained from Aldrich, Acros, or Strem Chemicals unless otherwise specified. Solvents were purchased from Fischer Scientific. Toluene and dichloromethane were dried through activated alumina columns. Tetrahydrofuran was distilled from sodium and benzophenone under N_2. Liquid substrates were distilled and degassed prior to use. B(pin)- substituted alkynes and *N*-(2-pyridyl) sulfonyl imines were prepared by literature methods. Dimethylzinc and diethylzinc were obtained from Akzo Nobel and 2.0 M solution in toluene were prepared and stored in a Vacuum Atmospheres drybox. NMR spectra were obtained on Brüker 300 or 500 MHz Fourier transform spectrometer at the University of Pennsylvania NMR facility. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were referenced to residual solvent. $^{11}B\{^{1}H\}$ NMR spectra were referenced to $BF_3 \cdot OEt_2$. The infrared spectra were obtained using a Perkin-Elmer 1600 series spectrometer. HRMS data was obtained on a Waters LC-TOF mass spectrometer (model LCT-XE Premier) using electrospray ionization in positive or negative mode, depending on analyte. Melting points were determined on a Uni-melt Thomas Hoover melting point

apparatus and are uncorrected. Thin-layer chromatography was performed on Whatman precoated silica gel 60 F-254 plates and visualized by ultraviolet light or by staining with ceric ammonium molybdate, phosphomolybdic acid, or potassium permanganate solutions. Silica gel (Silicaflash, P60, 40-63 μm, Silicycle) was used for flash chromatography.

Caution. *Dialkylzinc reagents are pyrophoric*. *Care must be used when handling them*.

Characterization of *N*-Pyridyl Sulfonyl Imine:

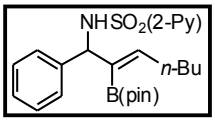


***N*-(2-Methoxybenzylidene)pyridine-2-sulfonamide (6).** The product was prepared according to literature procedure[14] using *o*-methoxybenzaldehyde (2.5 mmol, 0.34 g) to give the title compound as a crystalline solid (0.42 g, 74% yield). m.p. 111-114 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (s, 1H), 8.75 – 8.73 (m, 1H), 8.24 (d, J = 7.9 Hz, 1H), 8.08 (dd, J = 8.0, 1.7 Hz, 1H), 7.96 (td, J = 7.8, 1.7 Hz, 1H), 7.62-7.57 (m, 1H), 7.54 – 7.51 (m, 1H), 6.98 (d, J = 8.2 Hz, 2H), 3.95 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 170.5, 162.3, 156.5, 150.6, 150.1, 138.2, 137.7, 129.8, 127.3, 123.5, 121.1, 111.8, 56.0; IR (neat) 3430, 1639, 1588, 1479, 1324, 1254, 1172 cm^{-1}; HRMS m/z 277.0648 [$(MH)^+$; calcd for $C_{13}H_{13}N_2O_3S$: 277.0641].

Synthesis and Characterization of B(pin)-substituted Allylic Amines:

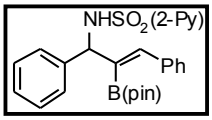
General Procedure A: Synthesis of B(pin)-substituted Allylic Amines. To a suspension of $HBCy_2$ (53.4 mg, 0.30 mmol) in toluene (1.0 mL) under N_2 was added alkyne-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane[25] (0.30 mmol) and the reaction mixture

was stirred for 30 min at rt, after which it was homogeneous. The reaction vessel was cooled to –78 °C and treated with Me_2Zn (0.15 mL, 2.0 M in toluene, 0.30 mmol) for 30 – 45 min. The solution was then warmed to –18 °C, and a solution of *N*-(2-pyridyl) sulfonyl imine (0.2 mmol) in dichloromethane (4 ml) was added slowly to the solution over 10 min. The reaction mixture was stirred at –18 °C until TLC showed complete consumption of the imines (5-18 h). The reaction mixture was warmed to 0 °C, diluted with EtOAc (2 mL) and quenched with saturated NH_4Cl (2 mL). The organic layer was separated and the aqueous solution was extracted with EtOAc (3 x 5 mL). The combined organic layer was dried over $MgSO_4$, filtered through Celite and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 80:20) to give the desired B(pin)-substituted allylic amine.

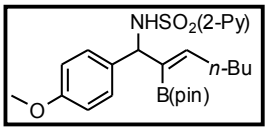


(*E*)-*N*-(1-Phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-2-enyl)pyridine-2-sulfonamide (1a). The product was prepared by General Procedure A using *N*-benzylidenepyridine-2-sulfonamide (49.3 mg, 0.2 mmol) and 2-hex-1-ynyl-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (62.4 mg, 0.3 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 80:20) to afford the title compound (73.0 mg, 80% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (dt, *J* = 4.7, 0.8 Hz, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.78 (td, *J* = 7.7, 1.2 Hz, 1H), 7.38 (dd, *J* = 7.6, 4.7 Hz, 1H), 7.27-7.26 (m, 2H), 7.19 (t, *J* = 7.6 Hz, 2H), 7.14-7.12 (m, 1H), 6.28 (d, *J* = 9.8 Hz, 1H), 5.98 (t, *J* = 7.5 Hz, 1H), 5.05 (d, *J* = 9.8 Hz, 1H), 2.26 – 2.15

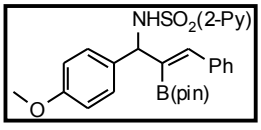
(m, 1H), 2.01 (m, 1H), 1.24 – 1.16 (m, 4H), 1.13 (s, 6H), 1.03 (s, 6H), 0.85 (t, J = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 158.7, 150.3, 150.1, 141.6, 137.7, 128.1, 127.0, 126.8, 126.3, 122.3, 83.6, 64.6, 31.8, 30.5, 24.9, 24.4, 22.4, 14.1 (the quaternary vinyl C bearing the boron group is not observed); $^{11}B\{^{1}H\}$ NMR ($CDCl_3$, 128 MHz) δ 28.6; IR (neat) 3312, 2977, 1634, 1427, 1339, 1178, 1141 cm^{-1}; HRMS m/z 457.2333 $[(MH)^+$; calcd for $C_{24}H_{34}BN_2O_4S$: 457.2327].



(*E*)-*N*-(1,3-Diphenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)pyridine-2-sulfonamide (1b). The product was prepared by General Procedure A using *N*-benzylidenepyridine-2-sulfonamide (49.3 mg, 0.20 mmol) and 4,4,5,5-tetramethyl-2-(phenylethynyl)-[1,3,2]-dioxaborolane (45.6 mg, 0.30 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 80:20) to afford the title compound (64.8 mg, 68% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 – 8.52 (m, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.66 (td, J = 7.8, 1.7 Hz, 1H), 7.35 (d, J = 7.3 Hz, 2H), 7.26 – 7.18 (m, 7H), 7.13 – 7.06 (m, 2H), 6.79 (s, 1H), 6.20 (d, J = 9.7 Hz, 1H), 5.29 (d, J = 9.7 Hz, 1H), 1.03 (s, 6H), 0.93 (s, 6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 158.1, 149.9, 144.3, 140.1, 137.4, 136.8, 128.6, 128.1, 128.0, 127.6, 127.2, 126.7, 126.1, 122.1, 83.9, 64.6, 24.4, 24.1 (the quaternary vinyl C bearing the boron group is not observed). $^{11}B\{^{1}H\}$ NMR ($CDCl_3$, 128 MHz) δ 28.7; IR (neat) 3304, 2978, 1627, 1494, 1427, 1335, 1177, 1141 cm^{-1}; ^{1}HRMS m/z 499.1828 $[(M+Na)^+$; calcd for $C_{26}H_{29}BN_2NaO_4S$: 499.1833].

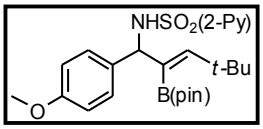


(*E*)-*N*-(1-(4-Methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-2-enyl)pyridine-2-sulfonamide (1c). The product was prepared by General Procedure A using *N*-(4-methoxybenzylidene)pyridine-2-sulfonamide (55.2 mg, 0.20 mmol) and 2-hex-1-ynyl-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (62.4 mg, 0.30 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 80:20) to afford the title compound as a white solid (84.6 mg, 87% yield). m.p. 108-111 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, *J* = 4.4 Hz, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.80 (td, *J* = 7.7, 1.7 Hz, 1H), 7.40 (ddd, *J* = 7.7, 4.7, 1.2 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 6.27 (d, *J* = 9.8 Hz, 1H), 5.95 (t, *J* = 7.6 Hz, 1H), 5.00 (d, *J* = 9.7 Hz, 1H), 3.76 (s, 3H), 2.24 – 2.13 (m, 1H), 2.08 – 1.95 (m, 1H), 1.32 – 1.23 (m, 2H), 1.23 – 1.17 (m, 2H), 1.15 (s, 6H), 1.06 (s, 6H), 0.86 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 158.4 (two overlapping carbon signals), 149.8, 149.5, 137.3, 133.6, 127.7, 125.9, 122.1, 113.2, 83.3, 63.8, 55.2, 31.5, 30.2, 24.7, 24.2, 22.1, 13.8 (the quaternary vinyl C bearing the boron group is not observed); ^{11}B{^{1}H} NMR ($CDCl_3$, 128 MHz) δ 30.5; IR (neat) 3310, 2958, 1611, 1511, 1427, 1339, 1250, 1177, 1141 cm^{-1}; HRMS m/z 509.2244 [$(M+Na)^+$; calcd for $C_{25}H_{35}BN_2NaO_5S$: 509.2252].



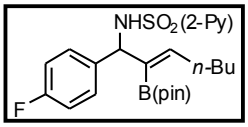
(*E*)-*N*-(1-(4-Methoxyphenyl)-3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)pyridine-2-sulfonamide (1d). The product was prepared by General Procedure A using *N*-(4-methoxybenzylidene)pyridine-2-sulfonamide (55.2 mg, 0.20 mmol) and 4,4,5,5-tetramethyl-2-(phenylethynyl)-1,3,2-

dioxaborolane (45.6 mg, 0.30 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 80:20) to afford the title compound as a white solid (94.1 mg, 93% yield). m.p. 145-147 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 – 8.54 (m, 1H), 7.89 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.67 (td, *J* = 7.7, 1.7 Hz, 1H), 7.27 – 7.20 (m, 6H), 7.11 – 7.09 (m, 2H), 6.78 – 6.75 (m, 3H), 6.15 (d, *J* = 9.7 Hz, 1H), 5.24 (d, *J* = 9.7 Hz, 1H), 3.76 (s, 3H), 1.05 (s, 6H), 0.96 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.0, 158.3, 150.1, 144.1, 137.7, 137.0, 132.4, 128.8, 128.2, 128.2, 127.9, 126.3, 122.4, 113.7, 84.1, 64.3, 55.5, 24.7, 24.4 (the quaternary vinyl C bearing the boron group is not observed); ^{11}B{^{1}H} NMR ($CDCl_3$, 128 MHz) δ 28.5; IR (neat) 3294, 2979, 1611, 1511, 1427, 1337, 1251, 1177, 1141 cm^{-1}; HRMS m/z 529.1932 [$(M+Na)^{+}$; calcd for $C_{27}H_{31}BN_2NaO_5S$: 529.1931].

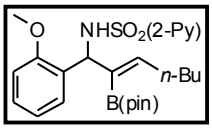


(*E*)-*N*-(1-(4-Methoxyphenyl)-4,4-dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-enyl)pyridine-2-sulfonamide (1e). The product was prepared by General Procedure A using *N*-(4-methoxybenzylidene)pyridine-2-sulfonamide (55.2 mg, 0.20 mmol) and 2-(3,3-dimethylbut-1-ynyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (62.4 mg, 0.30 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 80:20) to afford the title compound as a white solid (58.4 mg, 60% yield). m.p. 166-168 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, *J* = 4.3 Hz, 1H), 7.91 (d, *J* = 7.7 Hz, 1H), 7.80 (t, *J* = 7.4 Hz, 1H), 7.40 (dd, *J* = 7.4, 4.7 Hz, 1H), 7.21 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 6.12 (d, *J* = 9.2 Hz, 1H), 5.81 (s, 1H), 4.98 (d, *J* = 9.2 Hz, 1H), 3.75 (s, 3H), 1.03 (s. 6H), 1.01 (s, 6H), 0.91 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz,

$CDCl_3$) δ 158.9 (two overlapping carbon signals), 157.0, 150.2, 137.7, 133.1, 128.3, 126.3, 122.3, 113.6, 84.0, 65.3, 55.5, 33.6, 30.5, 24.8 (the quaternary vinyl C bearing the boron group is not observed); IR (neat) 3308, 2956, 1611, 1510, 1427, 1340, 1250, 1177, 1142 cm^{-1}; HRMS m/z 509.2247 [$(M+Na)^+$; calcd for $C_{25}H_{35}BN_2NaO_5S$: 509.4210].



(*E*)-*N*-(1-(4-Fluorophenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-2-enyl)pyridine-2-sulfonamide (1f). The product was prepared by General Procedure A using *N*-(4-fluorobenzylidene)pyridine-2-sulfonamide (52.8 mg, 0.20 mmol) and 2-hex-1-ynyl-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (62.4 mg, 0.30 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 80:20) to afford the title compound as a white solid (66.4 mg, 70% yield). m.p. 102-105 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 – 8.61 (m, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.81 (td, *J* = 7.7, 1.6 Hz, 1H), 7.41 (dd, *J* = 7.5, 4.7 Hz, 1H), 7.28-7.22 (m, 2H), 6.89 (t, *J* = 8.7 Hz, 2H), 6.29 (d, *J* = 9.8 Hz, 1H), 5.96 (t, *J* = 7.6 Hz, 1H), 5.01 (d, *J* = 9.8 Hz, 1H), 2.23-2.13 (m, 1H), 2.05 – 1.95 (m, 1H), 1.21 – 1.15 (m, 4H), 1.15 (s, 6H), 1.04 (s, 6H), 0.85 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 163.0, 161.0, 158.5, 150.6 (d, *J* = 60 Hz), 137.7, 137.5 (d, *J* = 2.9 Hz), 128.4 (d, *J* = 7.9 Hz), 126.4, 122.3, 114.9 (d, *J* = 21.4 Hz), 83.7, 64.0, 31.8, 30.4, 24.9, 24.4, 22.4, 14.1 (the quaternary vinyl C bearing the boron group is not observed); IR (neat) 3308, 2956, 1611, 1510, 1427, 1340, 1250, 1177, 1142 cm^{-1}; HRMS m/z 497.2055 [$(M+Na)^+$; calcd for $C_{24}H_{32}BFN_2NaO_4S$: 497.2052].

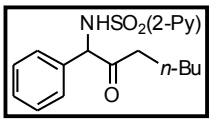


(*E*)-*N*-(1-(2-Methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-2-enyl)pyridine-2-sulfonamide (1g). The product was prepared by General Procedure A using *N*-(2-methoxybenzylidene)pyridine-2-sulfonamide (55.2 mg, 0.20 mmol) and 2-hex-1-ynyl-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (64.4 mg, 0.30 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 80:20) to afford the title compound as a oil (51.6 mg, 53% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 – 8.46 (m, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.65 (td, *J* = 7.7, 1.6 Hz, 1H), 7.29 – 7.22 (m, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.06 – 6.99 (m, 1H), 6.68 (t, *J* = 7.5 Hz, 1H), 6.60 (d, *J* = 8.2 Hz, 1H), 6.37 (d, *J* = 10.0 Hz, 1H), 6.01 (t, *J* = 7.6 Hz, 1H), 5.32 (d, *J* = 10.0 Hz, 1H), 3.68 (s, 3H), 2.17 – 2.07 (m, 2H), 1.23 – 1.15 (m, 16H), 0.84 (t, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 158.2, 156.5, 149.8, 147.1, 137.3, 128.8, 128.6, 128.3, 126.0, 122.3, 120.0, 110.5, 83.5, 59.6, 55.3, 31.9, 30.6, 25.1, 24.7, 22.3, 14.1 (the quaternary vinyl C bearing the boron group is not observed); IR (neat) 3308, 2957, 1600, 1493, 1427, 1343, 1246, 1178, 1142 cm^{-1}; HRMS m/z 509.2249 [$(M+Na)^{+}$; calcd for $C_{25}H_{35}BN_2NaO_5S$: 509.2252].

Synthesis and Characterization of α-Amino Ketones:

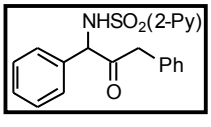
General Procedure B: Synthesis of α-Amino Ketones. To a solution of allylic amine boronate ester (0.10 mmol) in a 1:1 mixture of THF : H_2O (1 mL each) was added $NaBO_3 \cdot H_2O$ (0.30 mmol) at rt. The resulting suspension was stirred at rt until the reaction was complete by TLC (2–6 h). Water was added (1 mL) and the solution was extracted with Et_2O (3 x 10 mL). The combined diethyl ether phase was washed with brine, dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude

product was purified by flash column chromatography on silica gel to obtain the pure α-amino ketone.



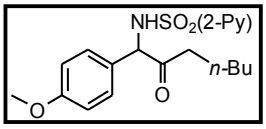
***N*-(2-Oxo-1-phenylheptyl)pyridine-2-sulfonamide (2a)**. The product was prepared by General Procedure B using **1a** (45.6 mg, 0.10 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 70:30) to afford the title compound as a white solid (27.7 mg, 80% yield). m.p. 100-102 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, J = 4.7 Hz, 1H), 7.67 – 7.62 (m, 2H), 7.35 – 7.28 (m, 1H), 7.22 – 7.15 (m, 3H), 7.14 – 7.09 (m, 2H), 6.37 (d, J = 6.3 Hz, 1H), 5.38 (d, J = 6.3 Hz, 1H), 2.41 – 2.22 (m, 2H), 1.51 – 1.44 (m, 1H), 1.42 – 1.35 (m, 1H), 1.18 – 1.11 (m, 2H), 1.10 – 1.02 (m, 2H), 0.78 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 204.5, 158.3, 149.8, 137.8, 135.4, 129.1, 128.8, 128.3, 126.5, 121.8, 66.5, 39.6, 31.2, 23.5, 22.4, 14.0; IR (neat) 3280, 2929, 2855, 1721, 1579, 1455, 1427, 1335, 1246, 1176, 1121 cm^{-1}; HRMS m/z 347.1435 [$(MH)^+$; calcd for $C_{18}H_{23}N_2O_3S$: 347.1424].

Synthesis of **2a** in a tandem procedure: After completion of the addition step as judged by TLC, the reaction was removed under vacuum pressure. THF/H_2O (1 mL each) was added followed by $NaBO_3 \cdot H_2O$ (29.9 mg , 0.30 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 70:30) to obtain the α-amino ketone as a white solid (23.5 mg, 68% yield).

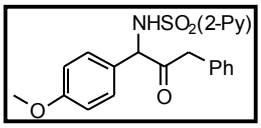


***N*-(2-Oxo-1,3-diphenylpropyl)pyridine-2-sulfonamide (2b).** The product was prepared by General Procedure B using **1b** (47.6 mg, 0.10

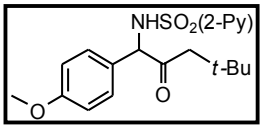
mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 70:30) to afford the title compound as a white solid (27.5 mg, 75% yield). m.p. 159-160 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 – 8.42 (m, 1H), 7.69 – 7.58 (m, 2H), 7.35 – 7.28 (m, 1H), 7.27 – 7.21 (m, 6H), 7.15 (dd, *J* = 7.4, 2.2 Hz, 2H), 6.96 (dd, *J* = 6.5, 2.8 Hz, 2H), 6.39 (s, 1H), 5.52 (s, 1H), 3.63 (s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 201.8, 158.1, 149.8, 137.8, 135.0, 132.8, 129.6, 129.3, 129.0, 128.9, 128.6, 127.5, 126.5, 121.7, 65.9, 46.2; IR (neat) 3138, 2906, 2851, 1724, 1580, 1456, 1427, 1340, 1178, 1120 cm^{-1}; HRMS m/z [(MH)$^{+}$; calcd for $C_{20}H_{19}N_2O_3S$: 367.1111].



***N*-(1-(4-Methoxyphenyl)-2-oxoheptyl)pyridine-2-sulfonamide (2c).** The product was prepared by General Procedure B using **1c** (48.6 mg, 0.10 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 70:30) to afford the title compound as a white solid (36.1 mg, 96% yield). m.p. 91-94 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 – 8.54 (m, 1H), 7.73 – 7.63 (m, 2H), 7.39 – 7.32 (m, 1H), 7.04 (d, *J* = 8.7, 1.4 Hz, 2H), 6.71 (d, *J* = 8.7, 1.3 Hz, 2H), 6.36 (d, *J* = 6.3 Hz, 1H), 5.34 (d, *J* = 6.4 Hz, 1H), 3.75 (s, 3H), 2.39 – 2.25 (m, 2H), 1.54 – 1.44 (m, 1H), 1.44 – 1.35 (m, 1H), 1.21 – 1.13 (m, 2H), 1.13 – 1.05 (m, 2H), 0.81 (t, *J* = 7.2, 1.2 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 204.7, 160.0, 158.4, 149.8, 137.8, 129.6, 127.4, 126.4, 121.9, 114.5, 65.8, 55.5, 39.5, 31.2, 23.5, 22.4, 14.0; IR (neat) 3273, 2928, 2857, 1718, 1609, 1512, 1427, 1340, 1254, 1176 cm^{-1}; HRMS m/z 377.1546 [(MH)$^{+}$; calcd for $C_{19}H_{25}N_2O_4S$: 377.1530].

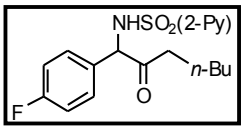


***N*-(1-(4-Methoxyphenyl)-2-oxo-3-phenylpropyl)pyridine-2-sulfonamide (2d)**. The product was prepared by General Procedure B using **1d** (50.6 mg, 0.10 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 70:30) to afford the title compound as a white solid (38.8 mg, 98% yield). m.p. 126-129 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, *J* = 4.6 Hz, 1H), 7.70 – 7.59 (m, 2H), 7.35 – 7.29 (m, 1H), 7.27 – 7.23 (m, 3H), 7.05 (d, *J* = 8.6 Hz, 2H), 6.97-6.97 (m, 2H), 6.74 (d, *J* = 8.6 Hz, 2H), 6.36 (d, *J* = 6.4 Hz, 1H), 5.45 (d, *J* = 6.1 Hz, 1H), 3.78 (s, 3H), 3.62 (s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 202.0, 160.1, 158.2, 149.8, 137.7, 132.9, 129.9, 129.6, 128.9, 127.5, 127.0, 126.4, 121.8, 114.6, 65.2, 55.5, 46.2; IR (neat) 3436, 3279, 3088, 2839, 1724, 1609, 1512, 1427, 1341, 1255, 1177, 1120 cm^{-1}; HRMS m/z 397.1229 [$(MH)^+$; calcd for $C_{21}H_{21}N_2O_4S$: 397.1217].

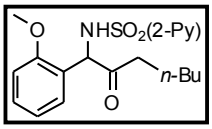


***N*-(1-(4-Methoxyphenyl)-4,4-dimethyl-2-oxopentyl)pyridine-2-sulfonamide (2e)**. The product was prepared by General Procedure B using **1e** (48.6 mg, 0.10 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 70:30) to afford the title compound as a oil (32.7 mg, 87% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (m, 1H), 7.71 – 7.60 (m, 2H), 7.36 – 7.31 (m, 1H), 7.02 (d, *J* = 8.7 Hz, 2H), 6.70 (d, *J* = 8.7 Hz, 2H), 6.40 (d, *J* = 6.2 Hz, 1H), 5.24 (d, *J* = 5.9 Hz, 1H), 3.74 (s, 3H), 2.29 (d, *J* = 15.7 Hz, 1H), 2.11 (d, *J* = 15.7 Hz, 1H), 0.89 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 203.6, 159.9, 158.4, 149.8, 137.7, 129.8, 127.2, 126.4, 121.9, 114.5, 66.8, 55.5, 51.6, 31.4, 29.7; IR (neat)

3275, 2955, 2870, 1720, 1609, 1512, 1427, 1341, 1254, 1177, 1121 cm^{-1}; HRMS m/z 399.1358 [$(M+Na)^+$; calcd for $C_{19}H_{24}N_2NaO_4S$: 399.1349].



***N*-(1-(4-Fluorophenyl)-2-oxoheptyl)pyridine-2-sulfonamide (2f)**. The product was prepared by General Procedure B using **1f** (47.4 mg, 0.10 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 70:30) to afford the title compound as a white solid (25.8 mg, 71% yield). m.p. 83-86 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 – 8.51 (m, 1H), 7.80 – 7.63 (m, 2H), 7.41 – 7.35 (m, 1H), 7.19 – 7.08 (m, 2H), 6.90 (t, *J* = 8.3 Hz, 2H), 6.43 (d, *J* = 6.2 Hz, 1H), 5.41 (d, *J* = 5.2 Hz, 1H), 2.44 – 2.22 (m, 2H), 1.57 – 1.46 (m, 1H), 1.45 – 1.41 (m, 1H), 1.23 – 1.15 (m, 2H), 1.13 – 1.03 (m, 2H), 0.81 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 204.3, 163.9 (d, *J* = 248 Hz), 158.3, 149.9, 137.9, 131.5 (d, *J* = 3.1 Hz), 130.2 (d, *J* = 8.4 Hz), 126.6, 121.8, 116.2 (d, *J* = 21.8 Hz), 65.7, 39.6, 31.2, 23.5, 22.4, 14.0; IR (neat) 3273, 2957, 2931, 2871, 1722, 1604, 1580, 1509, 1428, 1341, 1227, 1178, 1121 cm^{-1}; HRMS m/z 387.1150 [$(M+Na)^+$; calcd for $C_{18}H_{21}FN_2NaO_3S$: 387.1149].

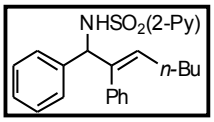


***N*-(1-(2-Methoxyphenyl)-2-oxoheptyl)pyridine-2-sulfonamide (2g).** The product was prepared by General Procedure B using **1g** (48.6 mg, 0.10 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 70:30) to afford the title compound as a oil (32.7 mg, 87% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.6 Hz, 1H), 7.73 – 7.65 (m, 2H), 7.35 – 7.29 (m, 1H), 7.22 – 7.15 (m, 1H), 7.12 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.81 (td, *J* = 7.5, 1.1 Hz, 1H), 6.70 – 6.67 (m, 1H), 6.35 (d, *J* = 7.5 Hz, 1H), 5.45 (d, *J* = 7.5 Hz, 1H), 3.72 (s, 3H),

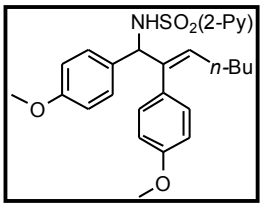
2.38 – 2.27 (m, 1H), 2.27 – 2.18 (m, 1H), 1.52 – 1.39 (m, 2H), 1.22 – 1.14 (m, 2H), 1.13 – 1.05 (m, 2H), 0.81 (t, J = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 204.4, 158.2, 156.8, 149.7, 137.7, 130.8, 130.2, 126.3, 124.2, 121.8, 121.1, 111.0, 63.3, 55.6, 38.8, 31.3, 23.6, 22.5, 14.0; IR (neat) 3284, 2958, 2858, 1724, 1600, 1580, 1494, 1464, 1342, 1252, 1177, 1120 cm^{-1}; HRMS m/z 377.1549 [$(MH)^+$; calcd for $C_{19}H_{25}N_2O_4S$: 377.1530].

Synthesis and Characterization of Trisubstituted 2-Arylated Allylic Amines:

General Procedure C: Suzuki Cross-Coupling of B(pin)-substituted Allylic Amines. To a Schlenk flask was added $Pd(OAc)_2$ (15 mol %) and PPh_3 (30 mol %) in 1 mL of dry and degassed THF at rt under N_2 and the solution stirred for 30 – 45 min. To this catalyst solution was added 2-B(pin)-substituted allylic amine (0.10 mmol), immediately followed by Cs_2CO_3 (0.30 mmol), 1 mL of degassed H_2O, and aryl bromide (0.30 mmol). The reaction mixture was heated in an oil bath at 75 °C until the B(pin)-substituted allylic amine had been fully consumed by TLC (12-24 h). The reaction was cooled to rt, diluted with EtOAc (1 mL) and saturated aqueous NH_4Cl (1 mL) was added. The organic layer was separated and the aqueous solution was extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered through Celite and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 80:20) to afford the trisubstituted allylic amine.

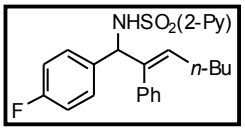


(*E*)-*N*-(1,2-Diphenylhept-2-enyl)benzenesulfonamide (3a). The product was prepared by General Procedure C using **1a** (45.6 mg, 0.10 mmol) and bromobenzene (31.6 μL, 0.30 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 80:20) to afford the title compound as a white solid (29.6 mg, 73% yield). m.p. 100-103 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 – 8.57 (d, *J* = 4.8 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.77 (td, *J* = 7.7, 1.7 Hz, 1H), 7.39 (ddd, *J* = 7.5, 4.6, 1.2 Hz, 1H), 7.20 – 7.15 (m, 6H), 7.14 – 7.09 (m, 2H), 6.81 – 6.75 (m, 2H), 5.62 (t, *J* = 7.4 Hz, 1H), 5.36 – 5.28 (m, 2H), 1.80 – 1.72 (m, 2H), 1.21 – 1.13 (m, 4H), 0.78 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 158.0, 150.2, 139.5, 137.8, 137.4, 131.6, 129.4, 128.4, 128.3, 127.6, 127.4 (overlapping carbon signals), 126.5, 122.3, 64.0, 31.9, 28.5, 22.4, 14.1; IR (neat) 3430, 2930, 1645, 1493, 1428, 1335, 1176 cm^{-1}; HRMS m/z 407.1794 [$(MH)^+$; calcd for $C_{24}H_{27}N_2O_2S$: 407.1788].



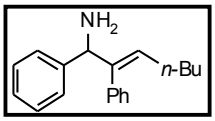
(*E*)-*N*-(1,2-Bis(4-methoxyphenyl)hept-2-enyl)benzenesulfonamide (3b). The product was prepared by General Procedure C using **1c** (48.6 mg, 0.10 mmol) and 4-methoxybromobenzene (37.7 μL, 0.30 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 80:20) to afford the title compound as a white solid (32.7 mg, 70% yield). m.p. 117-120 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, *J* = 3.6 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.79 (td, *J* = 7.7, 1.8 Hz, 1H), 7.47 – 7.35 (m, 1H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.85 – 6.60 (m, 6H), 5.55 (t, *J* = 7.3 Hz, 1H), 5.24 (s, 2H), 3.76 (s, 6H), 1.79 – 1.72 (m, 2H), 1.18 – 1.14 (m, 4H), 0.79 (t, *J* = 6.9

Hz, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 159.0, 158.8, 158.0, 150.2, 139.0, 137.8, 131.7, 131.2, 130.6, 129.6, 128.6, 126.5, 122.3, 113.8, 63.6, 55.4 (two overlapping carbon signals), 32.0, 28.5, 25.1, 22.4, 14.1; IR (neat) 3278, 2956, 2856, 1609, 1580, 1511, 1247, 1176 cm^{-1}; HRMS m/z 489.1806 $[(M+Na)^+$; calcd for $C_{26}H_{30}N_2NaO_4S$: 489.1818].



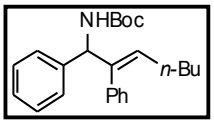
(*E*)-*N*-(1-(4-Fluorophenyl)-2-phenylhept-2-enyl)benzenesulfonamide (3c). The product was prepared by General Procedure C using **1f** (47.4 mg, 0.10 mmol) and bromobenzene (31.6 μL, 0.30 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 80:20) to afford the title compound (21.2 mg, 50% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60-8.54 (m, 1H), 7.89 – 7.72 (m, 2H), 7.48 – 7.34 (m, 1H), 7.22 – 7.15 (m, 3H), 7.16 – 7.03 (m, 2H), 6.86 (t, *J* = 8.6 Hz, 2H), 6.78 (dd, *J* = 6.5, 2.9 Hz, 2H), 5.59 (t, *J* = 7.4 Hz, 1H), 5.40 – 5.27 (m, 2H), 1.84 – 1.67 (m, 2H), 1.22 – 1.09 (m, 4H), 0.78 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 163.1, 161.2, 157.8, 150.2, 139.3, 137.9, 137.2, 135.4 (d, *J* = 3 Hz), 131.8, 129.4, 129.1 (d, *J* = 8.13 Hz), 128.4, 127.5, 126.6, 122.3, 115.3 (d, *J* = 21.1 Hz), 63.4, 31.8, 28.5, 22.4, 14.1; IR (neat) 3275, 2957, 2929, 2858, 1604, 1509, 1428, 1339, 1224, 1177 cm^{-1}; HRMS m/z $[(M+Na)^+$; calcd for $C_{24}H_{25}FN_2NaO_2S$: 447.1513].

Synthesis and Characterization of Trisubstituted 2-Arylated Allylic Primary Amine. Procedure for the *N*-Deprotection of the (2-Pyridyl)sulfonyl Group:



(*E*)-1,2-Diphenylhept-2-en-1-amine (4). To a solution of compound **3a** (40.6 mg, 0.10 mmol) in anhydrous methanol (4 mL) was added Mg power (24.0 mg, 1.0 mmol) at rt and the reaction mixture was stirred for 2 hr. Equal volumes of diethyl ether and saturated aq. NH_4Cl were added and the reaction was stirred for 30 minutes. The aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered through Celite and the solvent was removed under reduced pressure to give the crude primary amine (24.4 mg, 95% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.17 (m, 8H), 6.92 – 6.85 (m, 2H), 5.76 (t, *J* = 7.3 Hz, 1H), 4.79 (s, 1H), 1.95 – 1.84 (m, 4H), 1.37 – 1.30 (m, 2H), 1.29 – 1.22 (m, 2H), 0.82 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 144.5, 143.8, 139.3, 129.5, 128.4, 128.3, 128.0, 127.3, 127.0, 126.8, 62.2, 32.2, 28.6, 22.5, 14.1; HRMS m/z 249.1631 [$(M\text{-}NH_2)^+$; calcd for $C_{19}H_{21}$: 249.1638].

Synthesis and Characterization of Trisubstituted 2-Arylated Boc-protected Allylic Amine:



(*E*)-*N*-(1,2-Diphenylhept-2-enyl)pivalamide (5). Following the above procedure, compound **3a** (40.6 mg, 0.10 mmol) was transformed into the corresponding primary amine **4** which, without further purification, was subsequently dissolved in CH_2Cl_2 (2 mL) and treated with di-*tert*-butylcarbonate (65.4 mg, 0.30 mmol). The reaction mixture was stirred at rt until TLC showed complete consumption of the primary amine **4** (5-10 h). The reaction solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexanes:EtOAc = 80:20) to afford

the title compound as a white solid (30.7 mg, 88% yield). m.p. 55-57 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.26 – 7.19 (m, 6H), 6.95 (d, *J* = 7.1 Hz, 2H), 5.72 (t, *J* = 7.4 Hz, 1H), 5.51 (s, 1H), 4.89 (s, 1H), 2.00 – 1.85 (m, 2H), 1.44 (s, 9H), 1.38 – 1.28 (m, 2H), 1.29 – 1.20 (m, 2H), 0.82 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 155.1, 140.9, 140.8, 138.7, 129.8, 129.5, 128.6, 128.2, 127.4 (two overlapping carbon peaks), 127.0, 79.7, 61.1, 32.2, 28.6, 28.5, 22.4, 14.1; IR (neat) 3443, 2959, 2930, 2872, 1703, 1601, 1493, 1366, 1249, 1169; HRMS m/z 388.2263 [$(M+Na)^{+}$; calcd for $C_{24}H_{31}NNaO$: 372.2298].

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CHAPTER 4

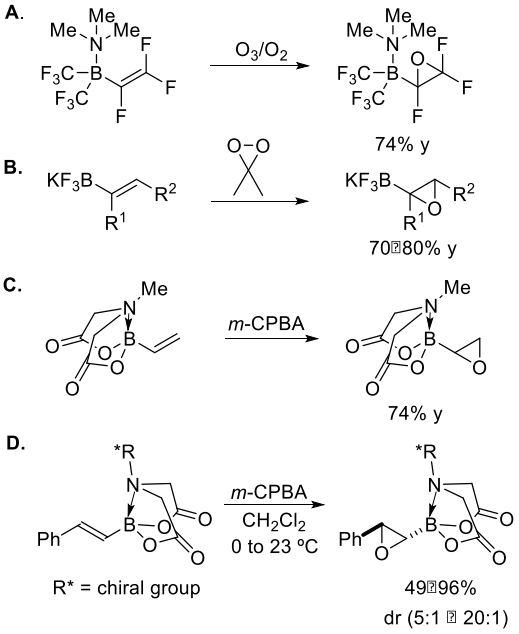
Chemo- and diastereoselective tandem dual oxidation of B(pin)-substituted allylic alcohols: synthesis of B(pin)-substituted epoxy alcohols, 2-keto-anti-1,3-diols and dihydroxy-tetrahydrofuran-3-ones[viii][ix]

1. Introduction:

The diverse reactivity of the B–C bond has led to innumerable applications in synthetic organic chemistry.[1-3] One of the most appreciated transformations of the B–C bond is its oxidation to afford alcohols.[4, 5] In the case of vinyl boron derivatives, the same oxidation affords ketones. In contrast to these oxidations, there are very few examples demonstrating a reversal of chemoselectivity in the oxidation of vinyl boron species leading to the epoxidation of C=C. One strategy to reverse the oxidation chemoselectivity of vinylboronates is to block oxidation at boron by employing 4-coordinate boron species. Brauer and Pawelke[6] disclosed the epoxidation and oxidative cleavage of $(Me_3N)B(CF_3)_2(CF=CF_2)$ with ozone and dioxygen (Scheme 1, A). In 2003 Molander and Ribagorda[7] demonstrated that vinyl trifluoroborates[3] underwent epoxidation with DMDO to provide epoxytrifluoroborates (Scheme 1, B). Uno, Gilles, and Burke[8] showed that vinyl *N*-methyliminodiacetic acid (MIDA) boronates also withstand epoxidation conditions with *m*-CPBA to furnish the terminal epoxide (Scheme 1, C). More recently, Burke and Li[9] extended this methodology to highly diastereoselective epoxidation of internal vinyl boronates bearing enantioenriched PIDA chiral auxiliary (Scheme 1, D).

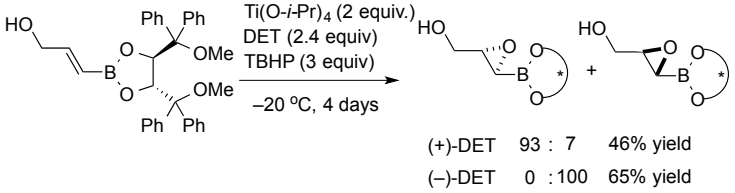
[viii] [N. Hussain, M. M. Hussain, P. J. Walsh, "*Chemo- and diastereoselective tandem dual oxidation of B(pin)-substituted allylic alcohols: synthesis of B(pin)-substituted epoxy alcohols, 2-keto-anti-1,3-diols and dihydroxy-tetrahydrofuran-3-ones*," Chem. Sci. **2013**,*4*, 3946-3957] – Reproduced by permission of The Royal Society of Chemistry.

[ix] This project was initiated by Dr. Mahmud Hussain.



Scheme 1: Oxidation of Four-coordinate Alkenyl Boron Derivatives.

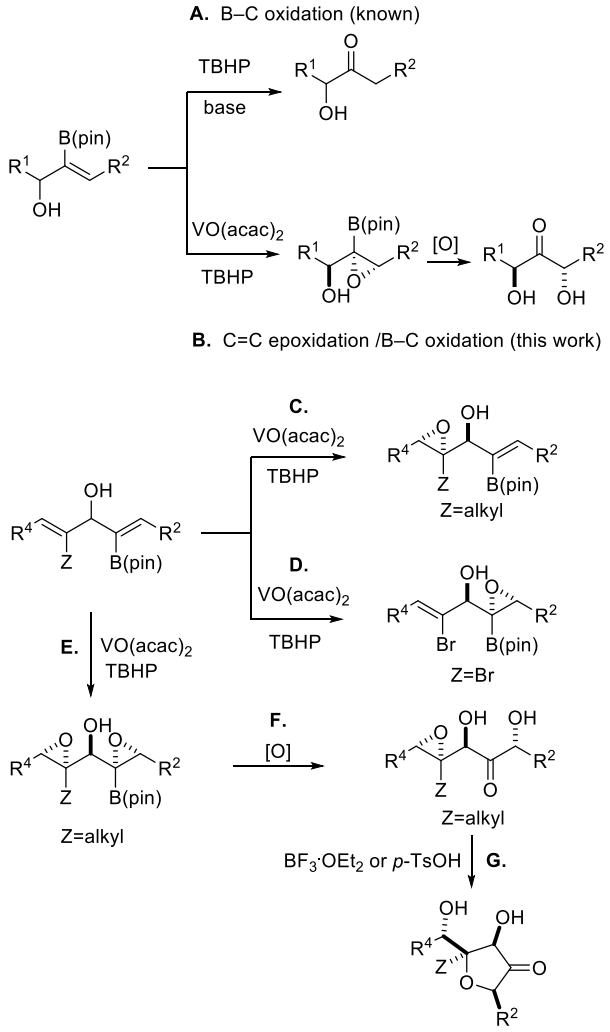
The results of Pawelke,[6] Molander,[7] Burke,[8, 9] and their co-workers raise several interesting questions. These include: 1) Is the chemoselective epoxidation of alkenyl boron substrates limited to 4-coordinate boron? and 2) Can the resulting boron-substituted epoxides be useful intermediates in organic synthesis? During our investigation into these questions, Pietruszka and co-workers[10] reported that a 3-coordinate vinyl boronate ester with bulky chiral auxiliaries could be epoxidized (Scheme 2). Poor diastereoselectivity (< 2:1) and low yields (40–52%) were obtained with achiral epoxidizing agents such as *m*-CPBA and $VO(acac)_2$/TBHP. Use of 2 equiv $Ti(O\text{-}i\text{-}Pr)_4$, 2.4 equiv (+)- or (–)-DET, and TBHP resulted in high diastereomeric ratios and moderate yields (46–65%) of the resulting epoxy alcohols.[10]



Scheme 2: Pietruszka and Co-workers' Epoxidation of Vinyl Boronate Esters with Stoichiometric Sharpless-Katsuki Catalyst.

Previously, our group reported the synthesis of 2-B(pin)-substituted allylic alcohols.[11] Under basic conditions, these intermediates underwent chemoselective oxidation of the B–C bond in the presence of TBHP and base (Scheme 3A).[11] Herein, we disclose an approach to reverse the chemoselectivity in the oxidation of vinylboronate esters via a highly chemo- and diastereoselective vanadium catalyzed epoxidation of readily available 2-B(pin)-substituted allylic alcohols (Scheme 3B). We probe, for the first time, the relative rates of epoxidation of allylic alcohols vs. B(pin)-substituted allylic alcohols using substrates possessing two allylic double bonds (Scheme 3C–D). A sequential diastereoselective epoxidation of the vinylboronate ester followed by B–C bond oxidation to provide 2-keto-*anti*-1,3-diols is introduced (Scheme 3B). When alcohols with both allylic and 2-B(pin)-substituted allylic double bonds were subjected to the tandem oxidation, bis-epoxides intermediates generated via pathway E yielded epoxy-substituted 2-keto-*anti*-1,3-diols with high diastereoselectivity (via F). Our work here provides novel oxidation chemistry of vinyl boronate esters, which can now be viewed as precursors to both ketones and α-hydroxy ketones.[12, 13] Finally, we describe an acid-mediated cyclization of four epoxide-substituted 2-keto-*anti*-1,3-diols (synthesized via F,

Scheme 3G) to provide fully substituted dihydroxy-tetrahydrofuran-3-ones as single diastereomers.

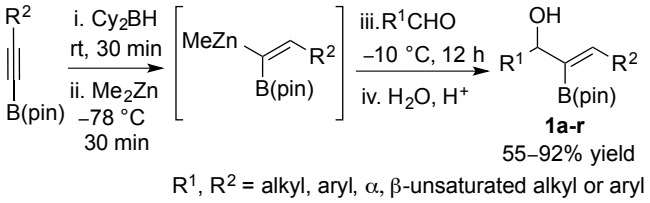


Scheme 3: Known B–C bond Oxidation of B(pin)-substituted Allylic Alcohols (A) and a new class of Stereoselective Oxidation Products via Chemo- and Diastereoselective Epoxidation or Dual Epoxidation/Oxidation Methodology (B); Application of these Reactions to Unsymmetrical Dienols (C–F); An acid-mediated Cyclization to Dihydroxy-tetrahydrofuran-3-ones (G).

2. Results and Discussion.

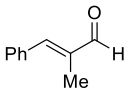
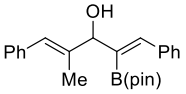
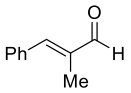
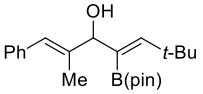
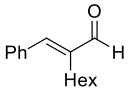
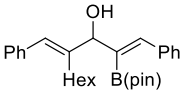
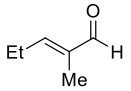
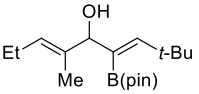
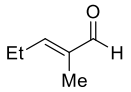
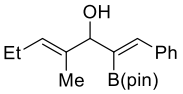
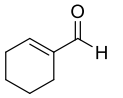
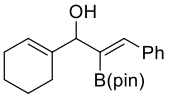
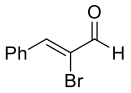
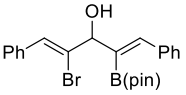
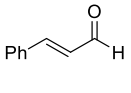
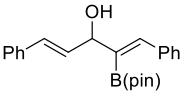
2.1. Synthesis of Substrates:

We recently reported[11, 12, 14] a straightforward one-pot synthesis of B(pin)-substituted allylic alcohols via functional group tolerant 1-alkenyl-1,1-bimetallic reagents[15] (Scheme 4). Employing air-stable B(pin)-substituted alkynes,[11, 14, 16, 17] hydroboration with dicyclohexyl borane affords the intermediate 1,1-diboro alkene.[18] The Cy_2B–C bond undergoes transmetallation significantly faster than the (pin)B–C bond,[19, 20] because in the latter the p-orbital on boron is partially filled by resonance donation from the adjacent oxygen lone pairs. Thus, transmetallation of the 1,1-diboro alkene with dialkylzinc reagents leads exclusively to the (*E*)-1-alkenyl-1,1-heterobimetalic intermediate, where the Zn–C bond exhibits much greater reactivity than the (pin)B–C bond.[11] Trapping the heterobimetallics with aldehydes and workup provides the 2-B(pin)-substituted allylic alcohols in 55–92% yield (Scheme 4).[12] The additions in Scheme 4 work well with various aliphatic and aromatic aldehydes as well as with diverse α,β-unsaturated aldehydes. Table 1 contains new bis-allylic alcohol substrates that were prepared for this study. It should be noted that no conjugate addition products were observed. Cinnamaldehyde derivatives typically gave excellent yields (85–92%, entries 1, 2, 7 and 8) whereas aliphatic and cyclic α,β-unsaturated aldehydes gave slightly lower yields (56–71%, entries 4–6). The bis-allylic alcohol substrates in Table 1 were all synthesized on gram scale.



Scheme 4: Generation and Trapping of 1-Alkenyl-1,1-Bimetallic Intermediates with Aldehydes.

Table 1: Synthesis of 2-B(pin)-substituted Bis-allylic Alcohols.[x]

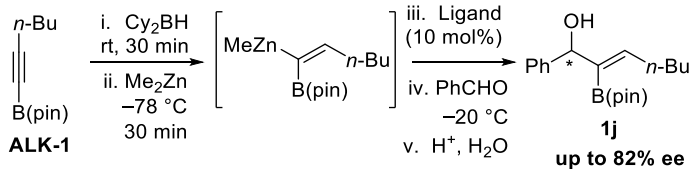
entry	aldehyde	allylic alcohol		yield (%)[a,b]
1.			**1k**	92
2.			**1l**	84
3.			**1m**	60
4.			**1n**	67
5.			**1o**	56
6.			**1p**	71
7.			**1q**	92
8.			**1r**	92

[a.] Isolated yields. [b.] All substrates synthesized on gram scale.

[x] Compound **1k** in Table 1 was synthesized by Dr. Mahmud Hussain.

2.2. Enantioselective Addition of 1-Alkenyl-1,1-heterobimetallic Reagents to Aldehydes.

Addition of 1,1-heterobimetallic borozinc intermediates to prochiral aldehydes in the presence of enantioenriched catalysts is expected to lead to optically active 2-B(pin)-substituted allylic alcohols. We have previously demonstrated the utility and versatility of these building blocks in a variety of highly stereoselective transformations.[11, 12, 14, 17, 21] Having developed a robust method for alkenyl heterobimetallic additions to aldehydes, we next sought to introduce an asymmetric variant of this reaction, as outlined below (Scheme 5).



Scheme 5: Asymmetric Addition of 1-Alkenyl-1,1-heterobimetallic to Benzaldehyde.

β-Amino alcohols form highly enantioselective catalysts in asymmetric addition of organozinc reagents to prochiral aldehydes.[22] One of the premier amino alcohol proligands is Nugent's 2-(*S*)-(–)-3-exo-(morpholino)isoborneol [(–)-MIB] **L1** (Table 2).[23-25] In the presence of catalytic amounts of MIB, organozinc reagents have been employed in highly enantioselective alkylation,[23, 24] vinylation,[26, 27, 28] ethoxy vinylation,[29] arylation,[30] and heteroarylation[31] of carbonyl compounds. We, therefore, initiated our

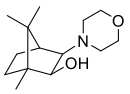
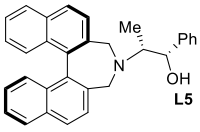
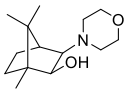
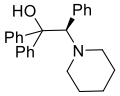
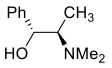
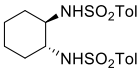
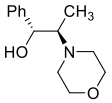
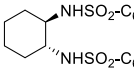
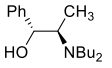
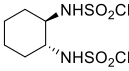
search for an enantioselective catalyst for alkenyl borozinc heterobimetallic addition to aldehydes by screening (–)-MIB and several other amino alcohols known to afford high stereoinduction in carbonyl addition reactions.

Following hydroboration of the B(pin) alkyne (**ALK-1**) and transmetallation to zinc (Scheme 5), the bimetallic intermediate was added to benzaldehyde in the presence of 10 mol % (–)-MIB at –20 °C. After workup, the 2-B(pin)-allylic alcohol **1j** was isolated in 65% yield with 62% ee (Table 2, entry 1). Slow addition of the aldehyde over 30 min improved the product ee to 70% (entry 2). The low enantioselectivities in these additions are surprising, because the MIB-based organozinc catalyst generally promotes the vinylation of benzaldehyde derivativess with >90% enantioselectivity. Given that B(pin)-substituted vinyl additions occur readily at –20 °C in the absence of catalyst, and that the enantioselectivity was improved at higher catalyst loading (80–82% ee with >40 mol % MIB), we speculate a fast background reaction was responsible for the poor stereoinduction. Based on this hypothesis, we examined additional catalysts in the addition of heterobimetallic reagents to benzaldehyde.

Ephedrine based amino alcohol ligands have been used in asymmetric vinylation of aldehydes to give allylic alcohols in high enantioselectivity.[20, 32] Employing 10 mol % **L2–L4**, however, imparted low enantioselectivities (entries 3–5). Next, we investigated **L5**, a binaphtho-azepine based amino alcohol developed by Chan and coworkers for asymmetric alkynylation of aldehydes.[33] In the presence of 10 mol % **L5**, the product was obtained in 42% ee (entry 6). Ligand **L6** bearing a tertiary alcohol moiety, synthesized by Pericàs[34] and coworkers and known to form a highly enantioselective

catalyst, generated the B(pin)-substituted allylic alcohol in 82% ee. Unfortunately the best yield we could obtain at this ee was 50%. We finally investigated a class of bis-sulfonamides, **L7–L9**, which are known to form highly enantioselective catalysts with organozinc reagents in the presence of titanium tetraisopropoxide.[35] In the presence of 10 mol % of bis-sulfonamides **L7–L9**, 1.2 equiv of Ti(O-*i*-Pr)$_4$ and 1.5 equiv of Me_2Zn, the resulting bis-sulfonamido-based catalysts failed to provide good enantioselectivities (entries 8–10).

Table 2: Enantioselective Addition of 1-Alkenyl-1,1-heterobimatallic Reagent to Benzaldehyde.[xi]

entry	ligand		ee (%)[a]	entry	ligand		ee (%)
1		**L1**	62 (65% y)	6		**L5**	42
2		**L1**	70[b] (70% y)	7		**L6**	82[b] (50% y)
3		**L2**	2	8		**L7**	2[c] (73% y)
4		**L3**	6	9		**L8**	7[c] (73% y)
5		**L4**	49	10		**L9**	12[c]

[a] Addition of aldehyde at −20 °C, using 10 mol% L*
[b] Slow addition of the aldehyde over 30 min at −30 °C
[c] Ligands screened with titanium tetraisopropoxide

With promising results obtained with (–)-MIB and Pericàs' ligand (entries 1, 2 and 7, Table 2), we attempted to further optimize several reaction parameters such as solvent (toluene, CH_2Cl_2, Et_2O and hexanes) and nature of the alkyl zinc reagents. Despite significant effort, higher enantioselectivities and better yields were not obtained.

[xi] Enantioselective Addition reactions were done by Dr. Mahmud Hussain.

Based on these results, we chose to proceed with the development of the methods outlined herein with racemic 2-B(pin)-substituted allylic alcohols.

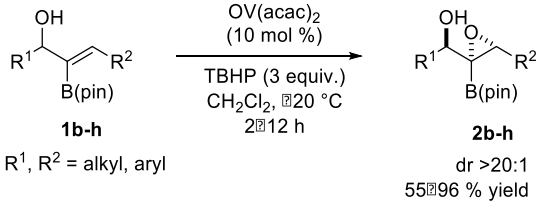
2.3. Chemoselective Epoxidation of Vinyl Boronate Esters.

With a series of racemic B(pin)-substituted allylic alcohol substrates prepared, we next focused on the chemoselective oxidation of vinyl boronate esters. As mentioned in the Introduction, we had previously shown that treatment of the intermediate allylic zinc alkoxides with TBHP resulted in oxidation of the B–C bond to furnish α-hydroxy ketones.[11] Our hypothesis was that the chemoselectivity of the oxidation could be redirected to favor epoxidation by employing transition metal-based catalysts.

Optimization of the reaction parameters (catalyst, solvent, temperature, stoichiometry, rate of addition, etc) were performed for the $OV(acac)_2$-catalyzed[36] epoxidation of 2-B(pin)-substituted allylic alcohols. The details are summarized in our initial communication.[12] In the presence of 10 mol% of $OV(acac)_2$ and 3 equiv of TBHP at –20 °C in dichloromethane, the 2-B(pin)-substituted allylic alcohols (**1b–h**) were rapidly converted to 2-B(pin)-substituted epoxy alcohols (**2b–h**) as single diastereomers by ^1H NMR spectroscopy (Scheme 6). Workup was performed by concentrating the reaction mixture under reduced pressure and rapid purification on silica gel to furnish the B(pin)-substituted epoxy alcohols as single diastereomers, albeit in low yields (typically 30–40%). It was soon realized that these 3-coordinate boron-substituted oxiranes readily decompose in the presence of trace acid or Lewis acidic silica gel under air. Fortunately, the crude products were very clean and required only filtration through a small pad of silica gel or Celite to remove the byproducts.

2.3.1. Substrate Scope of the Epoxidation of B(pin)-substituted Allylic Alcohols.

With the optimized conditions in hand, the scope of the epoxidation of B(pin)-substituted allylic alcohols was examined (Scheme 6). As anticipated from the results above, the B(pin)-substituted epoxides readily decompose even when rapidly chromatographed on silica gel. To maximize the epoxide yields, upon consumption of the B(pin)-substituted allylic alcohols (as judged by TLC), the reaction mixtures were concentrated and the crude products quickly filtered through a pad of silica gel or Celite. This method provided the epoxides in >90% purity (Scheme 6). In several cases the allylic alcohol was converted to the epoxide product without noticeable byproduct formation (^{1}H NMR), facilitating isolation and purification of the B(pin)-substituted epoxides.[12] The *anti*-relationship between the hydroxyl and epoxide is expected due to minimization of $A^{1,2}$-strain in the directed diastereomeric epoxidation transition states.[37, 38] The predicted relative stereochemistry was confirmed by single crystal X-ray analysis of 2d ($R^1 = CH_2CH_2Ph$, $R^2 = t$Bu).



Scheme 6: Chemo- and Diastereoselective Epoxidation of B(pin)-substituted Allylic Alcohols.

2.3.2. Bis-epoxidation of B(pin)-substituted Bis-allylic Alcohols.

Bis-epoxidation of dienols serves as a route to polyoxygenated compounds. With this in mind, we examined the epoxidation of B(pin)-substituted bis-allylic alcohols using

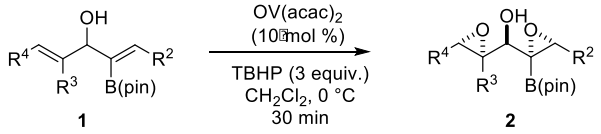
similar conditions as in Scheme 6. The results are depicted in Table 3. Thus, employing 10 mol % $OV(acac)_2$ and 3 equiv of TBHP at 0 °C smoothly epoxidized B(pin)-substituted bis-allylic alcohols to the corresponding B(pin)-substituted bis-epoxy alcohols. It is noteworthy that this bis-epoxidation generates four new stereocenters and furnishes novel bis-epoxides in good yields and excellent diastereoselectivity (dr >20:1).[39] We chose α,β-unsaturated aldehydes with α-substituents that would lead to α-substituted allylic alcohols (Table 3). It is known that epoxidation of allylic alcohols lacking either $A^{1,2}$ or $A^{1,3}$ strain lead to little or no diastereoselectivity.[37, 38, 40, 41] In fact, vanadium-catalyzed epoxidation of bis-allylic alcohol **1r** (Table 1, entry 8) gave a mixture of diastereomers (1.4:1) due to lack of either $A^{1,2}$ or $A^{1,3}$ strain in the diastereomeric epoxidation transition states. In contrast, the bis-epoxidations in Table 3 lead to single diastereomers in each case (^{1}H NMR). The bis-epoxidation reactions typically required 30 min to reach completion with the exception of **1m**, which required 2 h. The bis-epoxides were obtained in 69–90% yield despite the purification challenges (Table 3).

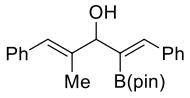
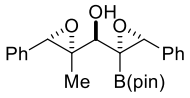
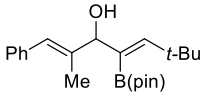
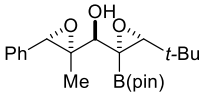
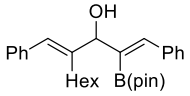
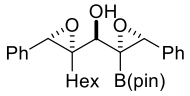
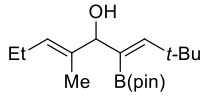
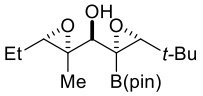
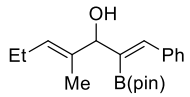
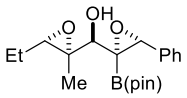
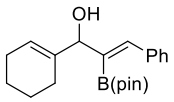
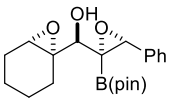
2.3.3. Chemoselective Mono Epoxidation of B(pin)-substituted Bis-allylic Alcohols.

Chemoselectivity is one of the most important challenges in synthetic organic chemistry. The successful epoxidation of both the vinyl groups in B(pin)-substituted bis-allylic alcohols positioned us to probe the chemoselectivity in the vanadium-catalyzed epoxidation of the two vinyl groups in the bis-allylic alcohols **1k–q**. Vinyl epoxy alcohols are versatile synthetic intermediates and have been widely used in the synthesis of natural products, such as *exo*- and *endo*-brevicomin,[42] the anticancer agent EBC-23

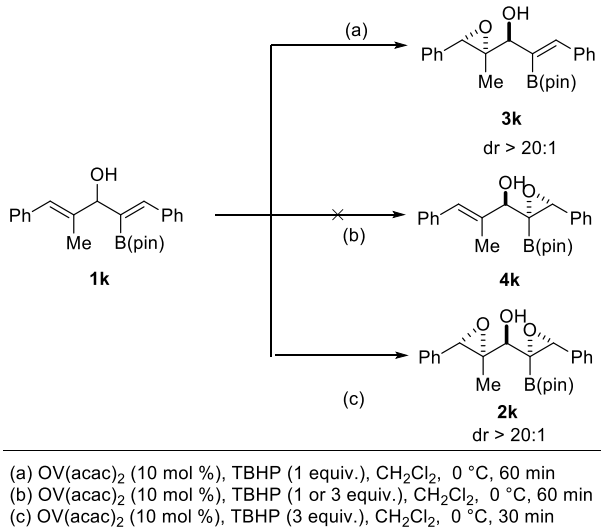
found in Australian tropical rainforests,[43] Isoaspinonine,[44] and the potent immunosuppressant antibiotic FK506.[45]

Table 3: Chemo- and Diastereoselective Epoxidation of B(pin)-substituted Bis-allylic Alcohols.



entry	allylic alcohol	product		dr	yield (%)
1.			**2k**	>20:1	69[a]
2.			**2l**	>20:1	72[a]
3.			**2m**	>20:1	86[b,c]
4.			**2n**	>20:1	88[c]
5.			**2o**	>20:1	90[c]
6.			**2p**	>20:1	82[c]

[a] Yields after chromatographic purification. [b] Reaction took 2 h for completion. [c] Yield determined by ^{1}H NMR analysis of crude mixture with internal standard CH_2Br_2; no chromatographic purification was necessary.



Scheme 7: Chemo-, Diastereo- and Regioselective Epoxidation of B(pin)-substituted Bis-Allylic Alcohols.

We hypothesized that the electrophilic nature of the oxovanadium (V) peroxide intermediate[46] would enable the catalyst to differentiate between the two vinyl groups based on electronics, favoring epoxidation of the more electron rich vinyl group. Despite the lower electronegativity of boron relative to carbon, the B(pin) group was anticipated to act as a π-acid and remove electron density from the double bond. Furthermore, the large size of B(pin) is anticipated to slow epoxidation proximate to boron. To explore our hypothesis, the relative barriers for epoxidation of model alkenes bearing methyl and boron groups were computed at the B3LYP/6-31G(d)[47] level in gas phase and at the (M06-2X/6-311G(d,p)[48] level in dichloromethane (CPCM;UFF).[49] These preliminary calculations indicate that the epoxidation at the methyl-substituted alkene is more favorable than the epoxidation at the boron-substituted alkene (see Supporting Information for details). Consistent with the computational study, subjecting the bis-allylic alcohol **1k** to 1.0 equiv of TBHP in the presence of 10 mol % $OV(acac)_2$ resulted

in the chemoselective oxidation of the C=C(alkyl) bond to afford the vinyl-B(pin) substituted epoxy alcohol 3k with high diastereoselectivity (Scheme 7, path a). No epoxidation of the C=CB(pin) bond was observed. Increasing the amount of TBHP to 1.5 equiv led to a mixture of mono-epoxide **3k** and bis-epoxide **2k**. As outlined above, further increasing the TBHP to 3.0 equiv yielded exclusively the bis-epoxide product 2k. Our optimal conditions entailed slow addition of TBHP over 30 min using a syringe pump to a solution of bis-allylic alcohol **1k** and 10 mol % $OV(acac)_2$ in dichloromethane solvent at 0 °C. The reaction required 40–60 min to reach completion.

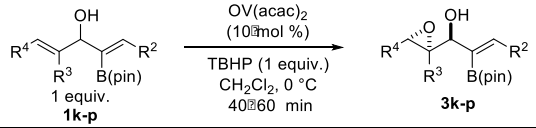
Having developed a method for the selective epoxidation of B(pin)-substituted bis-allylic alcohols, we set out to examine the substrate scope of this reaction.

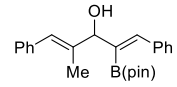
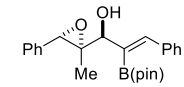
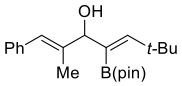
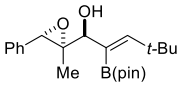
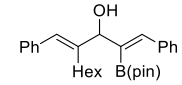
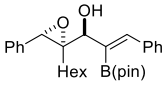
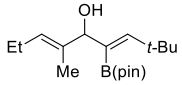
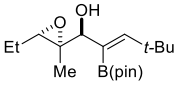
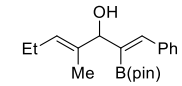
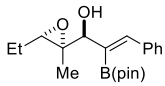
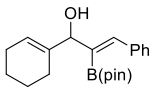
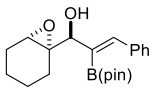
2.3.4. Substrate Scope of the Mono-epoxidation of B(pin)-substituted Bis-allylic Alcohols.

With the optimized conditions for the mono-epoxidation of 2-B(pin)-substituted bis-allylic alcohols in hand, the scope of the reaction was examined. The epoxidation worked well with methyl and *n*-hexyl substituents at the α-position (entries 1–3, Table 4). For the *n*-hexyl group (entry 3), 0.8 equiv of TBHP was employed because use of 1 equiv of TBHP gave mixtures of mono- and bis-epoxy alcohols. Both aromatic and aliphatic B(pin)-substituted bis-allylic alcohols were good substrates. Yields were lower for product **3o** and the cyclohexenyl derivative **3p** due to more challenging purifications via silica gel chromatography. Substoichiometric amounts of TBHP (0.7 equiv) were used in entries 4–6 to avoid formation of bis-epoxides. The *anti*-relationship between the

hydroxyl and epoxide is expected due to minimization of $A^{1,2}$-strain in the directed diastereomeric epoxidation transition states.[37, 39, 50]

Table 4: Chemo-, Diastereo- and Regioselective Mono-epoxidation of Bis-allylic Alcohols.



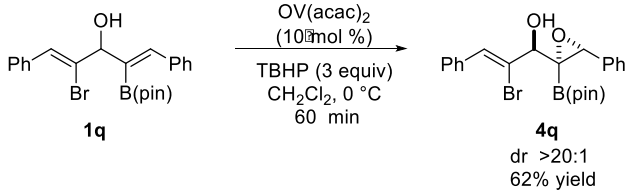
entry	allylic alcohol		product		dr	yield (%)[a]
1.		**1k**		**3k**	>20:1	69[b]
2.		**1l**		**3l**	>20:1	90[b]
3.		**1m**		**3m**	>20:1	70[b](86)[c,e]
4.		**1n**		**3n**	>20:1	63[b](75)[d,e]
5.		**1o**		**3o**	>20:1	54[b,d]
6.		**1p**		**3p**	>20:1	52[b,d]

[a] Isolated yields based on TBHP amount used. [b] Yields after chromatographic purification. [c] 0.8 equiv. of TBHP used. [d] 0.7 equiv. of TBHP used. [e] Yield determined by ^{1}H NMR analysis of crude mixture with internal standard CH_2Br_2.

2.3.5. Reversal of Chemoselectivity with Halide-substituted Allylic Alcohols.

The chemoselective epoxidation of vinyl groups in the presence of vinyl boronate esters led us to ask whether we could manipulate the electronics of the two vinyl groups to redirect the oxidant towards the vinyl boronate ester moiety. We envisioned that an electron deficient vinyl group would steer the reactivity toward the vinyl boronate ester π-system. Preliminary calculations, performed as outlined above were carried out to predict the relative barriers for epoxidation of model alkenes bearing the boro and bromo

groups. The calculations indicate that the epoxidation at the boron-substituted alkene is more favorable than the epoxidation at the bromo-substituted alkene (see Supporting Information for details). Therefore, **1q** (Table 1, entry 7) was treated with 3 equiv of TBHP in the presence of catalytic $OV(acac)_2$. The reaction went to completion with the formation of **4q** in 62% isolated yield as a single diastereomer (Scheme 8).[39]



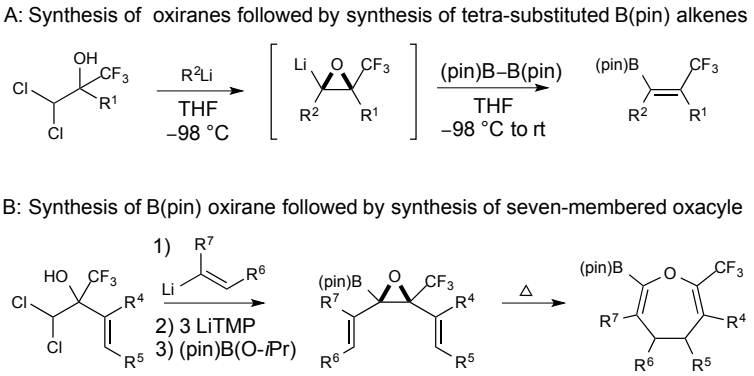
Scheme 8: Chemoselective Epoxidation at the Vinyl Boronate Ester Moiety of a-Bromo-vinyl Substituted B(pin) Bis-allylic Alcohol.

With reliable routes to form the B(pin)-substituted epoxides, we then focused on development of methods for stereoselective synthesis employing these epoxides as key intermediates.

2.4. Oxidation of B(pin)-substituted Epoxides.

Boron-substituted epoxides are versatile intermediates employed in a variety of novel transformations. They are formed as transient intermediates upon quenching lithiated epoxides with bis(pinacolato)diboron (Scheme 9A).[51, 52, 53] The final products of these reactions are olefins,[51, 52] diols and triols.[53] Shimizu and Hiyama quenched a lithiated epoxide with (pin)B(O-*i*-Pr) and isolated the resulting divinyl B(pin)-substituted epoxide. Upon heating, the epoxide underwent a Cope rearrangement to form a seven membered oxacycle (Scheme 9B).[54] Burke and Li recently employed PIDA-boronate substituted epoxides in the synthesis of small chiral medicinal building-blocks, such as a

glucagon receptor antagonist.[9] These reports attest to the diverse reactivity of boron-substituted epoxides.

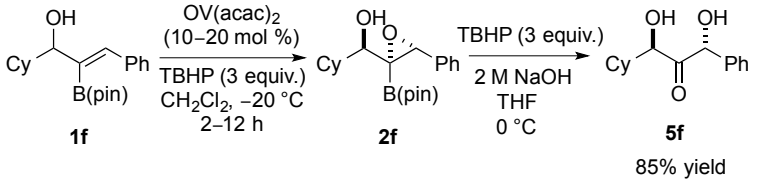


Scheme 9: Stereoselective Synthesis of Tetra-substituted Alkenyl Boronates.

2.4.1. Optimization of the Oxidation of B(pin)-substituted Epoxy Alcohols.

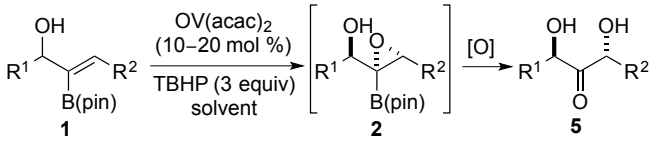
With the successful epoxidation of B(pin)-substituted allylic alcohols, we envisioned that further oxidation of the B(pin)-substituted epoxides would provide access to 2-keto-*anti*-1,3-diols. 2-Keto-*anti*-1,3-diols can be precursors for polyoxygenated carbon chains that are common structural motifs in natural products, such as sugars.[55] Given the high sensitivity of the B(pin) epoxides to silica gel, a tandem diastereoselective epoxidation/B–C bond oxidation of 2-B(pin)-substituted allylic alcohols was desired to circumvent the isolation of the epoxide intermediates. Toward development of this tandem reaction, we initially focused on oxidation of the B–C bond in isolated B(pin)-substituted epoxides (Scheme 10). Using 3 equiv TBHP, the substrate **2f** was treated with 2 M NaOH in THF solvent at 0 ^{o}C to cleanly provide the keto diol **5f** in 85% yield. Unfortunately, however, the tandem C=C/B–C oxidation in THF solvent gave multiple products, probably due to complications in the epoxidation step (Table 5, entry 1).

Switching to dichloromethane for the $OV(acac)_2$/TBHP epoxidation of **1f** followed by addition of 2 M NaOH to the intermediate epoxide **2f** generated the keto diol **5f**. The oxidation of **2f**, however, was very slow and did not reach completion in 18 h (entry 3). Conducting the epoxidation of **1f** in dichloromethane followed by addition of THF and 2 M NaOH to the intermediate epoxide **2f** resulted in consumption of the epoxide in 8 h and generation of the keto diol **5f** (entry 4). Other oxidants for the B–C oxidation such as aqueous hydrogen peroxide and sodium perborate[5] were evaluated and performed comparably (entry 5–7). With these optimized conditions, we examined the scope of the tandem epoxidation/B–C bond oxidation.



Scheme 10: Oxidation of B(pin)-substituted Allylic Alcohols to form 2-Keto-*anti*-1,3-diols.

Table 5: Optimization of the Tandem Epoxidation/B–C Bond Oxidation.

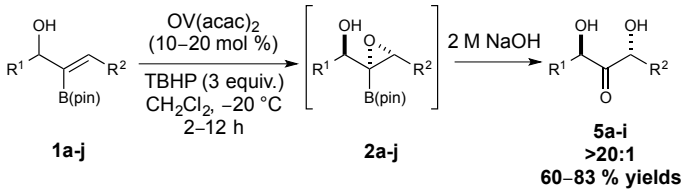


entry	R	R^1		solvent	oxidant	yield (%)[a]
1.	Cy	Ph	**1f**	THF	TBHP/NaOH	messy
2.	Cy	Ph	**1f**	Et_2O	TBHP/NaOH	messy
3.	Cy	Ph	**1f**	CH_2Cl_2	TBHP/NaOH	60–70
4.	Cy	Ph	**1f**	CH_2Cl_2/THF	TBHP/NaOH	75
5.	Cy	Ph	**1f**	CH_2Cl_2/THF	H_2O_2/NaOH	60–70
6.	*t*-Bu	*t*-Bu	**1c**	CH_2Cl_2/THF/H_2O	$NaBO_3{\cdot}H_2O$	83
7.	$Ph(CH_2)_2$	*t*-Bu	**1d**	CH_2Cl_2/THF/H_2O	H_2O_2/NaOH	81

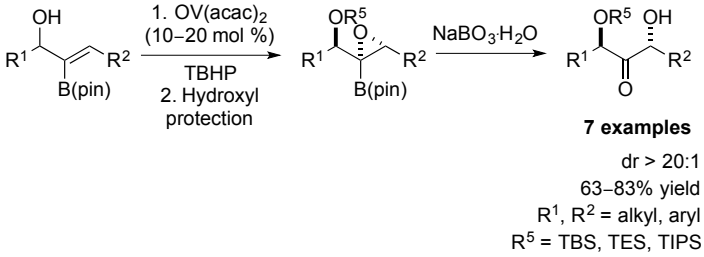
[a] Isolated yields.

2.4.2. Substrate Scope of the Tandem Epoxidation/B–C Bond Oxidation.

Using the optimized conditions in Table 5 (entries 6 and 7) the tandem reaction afforded keto diols with good yields and was tolerant of large and small alkyl substituents and aromatic substitutents at the carbinol and in the vinylic positions (60–83% yield, Scheme 11). It is worthy of note that the ketodiols were formed as single diastereomers, suggesting that epimerization of the α-carbons did not occur under our basic reaction conditions. The oxidation of the B–C bond most likely proceeds via attack of the deprotonated TBHP on the boron and migration of the boron bound carbon to oxygen to form the C–O bond. The strained ketal intermediate then opens with retention of configuration at the newly formed α-carbon. Consistent with this mechanism, crystal structures determination of **5c** (R^1, R^2= *t*Bu) and 5f (R^1=Cy, R^2=Ph) exhibit an *anti*-relationship between the hydroxyl groups.[12] The results indicate that *using the same oxidant (TBHP) and directing the initial oxidation to the B–C bond or the C=C bond, either α-hydroxy ketones (Scheme 3A) or 2-keto-anti-1,3-diols (Scheme 11) can be prepared with excellent chemoselectivity*. The mechanistic difference between the two oxidation reactions allowed us to further couple the chemoselective dual oxidation to a hydroxyl group protection transformation to furnish monoprotected 2-keto-*anti*-1,3-diols (Scheme 12).[12] It would be difficult to obtain the same products via chemoselective protection of one of the hydroxyl groups of 2-keto-*anti*-1,3-diol.



Scheme 11: Tandem C=C/B–C Oxidation of B(pin)-substituted Allylic Alcohols to Keto Diols.



Scheme 12: Epoxidation of B(pin)-substituted Allylic Alcohols followed by Protection and Oxidation.

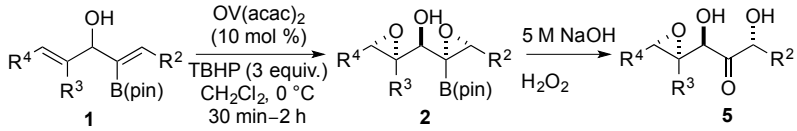
2.4.3. Oxidation of B(pin)-substituted Bis-epoxides.

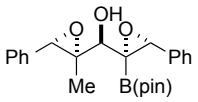
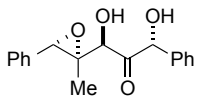
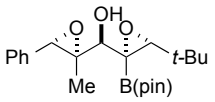
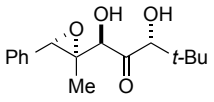
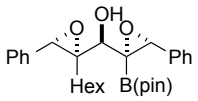
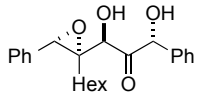
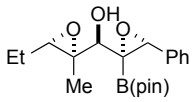
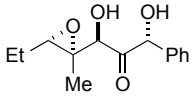
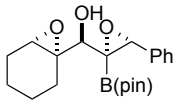
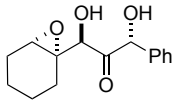
With a successful tandem epoxidation/B–C bond oxidation, we next turned our attention toward the oxidation of more challenging B(pin)-substituted bis-epoxides **2k**–**p**, which would provide access to epoxide-substituted 2-keto-*anti*-1,3-diols **5k**–**p**. Epoxy-keto-1,3-diols are important motifs in biologically active natural products such as chemomycin A, which possesses antitumor activity against human cancer cells.[56]

For the synthesis of epoxy-keto-*anti*-1,3-diols, B(pin)-substituted bis-epoxy alcohols were generated as shown in Table 3. The crude products were quickly filtered through a pad of silica gel, concentrated and re-dissolved in THF for the subsequent B–C bond oxidation. We evaluated three reagents for the oxidative B–C bond cleavage, namely basic TBHP, sodium perborate and basic hydrogen peroxide. Treatment of substrate **2k** with $NaBO_3{\cdot}H_2O$ at rt cleanly provided the epoxy keto diol **5k** in 78% yield

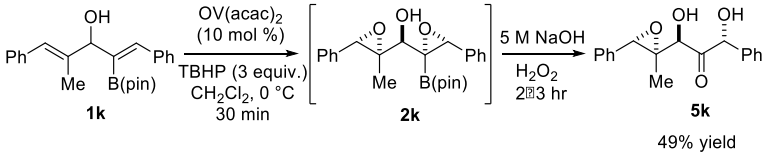
(entry 1, Table 6). Similar conditions smoothly furnished the bulky *tert*-butyl-substituted epoxy-keto-diol 5l (entry 2, 78% yield). Using 3.3 equiv of 30% H_2O_2 and 1.1 equiv of 5 M NaOH, epoxy-keto-diols **5o** and **5p** were obtained in moderate yields (entry 4 and 5). Comparable results were obtained when treated with basic TBHP (section 2.4.1); however, the keto diols were obtained in slightly lower yields. Tandem epoxidation/B–C bond oxidation of B(pin)-substituted bis-allylic alcohol was also examined. Conducting the epoxidation of **1k** in dichloromethane followed by addition of THF and 5 M NaOH to the intermediate epoxide **2k** resulted in consumption of the epoxide in 2–3 h and generation of the epoxy-keto-diol **5k** in 49% isolated yield (Scheme 13). The epoxy-keto-diols were again formed as single diastereomers, suggesting that epimerization of the α-carbons did not occur under the basic reaction conditions.[39] Importantly, these epoxy-keto-*anti*-1,3-diols containing bulky *tert*-butyl groups or aryl substituents (Table 6) cannot be accessed via the carbonyl α-alkylation chemistry developed by Enders and coworkers (Scheme 14).[57]

Table 6: Two Step Oxidation of B(pin)-substituted Allylic Alcohols to Form Epoxy-2-keto-*anti*-1,3-diols.

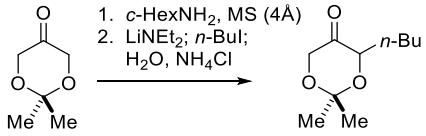


entry	bis-epoxide		epoxide-1,3-ketodiol		dr	yield (%)[a]
1.		**2k**		**5k**	>20:1	78[b]
2.		**2l**		**5l**	>20:1	78[b]
3.		**2m**		**5m**	>20:1	64
4.		**2o**		**5o**	>20:1	60
5.		**2p**		**5p**	>20:1	61

[a] Isolated yields. [b] Oxidation with $NaBO_3{\cdot}H_2O$, see SI for details.



Scheme 13: Tandem Epoxidation/B–C Bond Oxidation of B(pin)-substituted Bis-allylic Alcohol.



Scheme 14: S_N2-type α-Alkylation of Dihydroxyacetone Derivatives Developed by Enders and Co-workers.

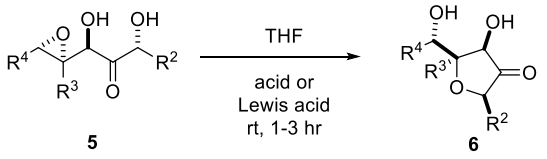
2.5. Diastereoselective Synthesis of Fully Substituted Dihydroxy-tetrahydrofuran-3-ones.

With reliable routes to synthesize the epoxy-2-keto-*anti*-1,3-diols (Table 6), we then focused on development of methods for stereoselective synthesis employing these compounds as key intermediates. We envisioned that intramolecular cyclization of our epoxy-keto-diols would furnish fully substituted dihydroxy-tetrahydrofuran-3-ones. Tetrahydrofuran-3-one motifs exist in a variety of natural products, such as scabrolides and pectenotoxins (PTX), which exhibit strong cytotoxic activity against the growth of human cancer cells.[58] Tetrahydrofuran derivatives have also been employed in the synthesis of nucleosides.[59] Tetrahydrofurans and related compounds are typically synthesized by intramolecular cyclization of epoxy alkanols, where the 5-exo mode of cyclization is favored due to the low ring strain of the tetrahydrofuranyl alcohol products.[60] Controlling the regio- and diastereoselectivity of the cyclization can be a challenge, because it is influenced by the nature of the epoxide substrate, reagents and catalysts employed in the reaction.[60] Few other methods for the synthesis of fully substituted tetrahydrofuran-3-ones have been developed. One well-known method of synthesizing tetrahydrofuran-3-ones is the utilization of diazo ketones in the presence of rhodium catalysts. This method frequently gives low yields and mixtures of stereoisomers.[61, 62] Substituted tetrahydrofuran-3-ones were also synthesized by singlet-oxygen-mediated reactions using 2-(β-hydroxyalkyl) furans[63] and by radical carbonylation/reductive cyclization using organochalcogen precursors.[62] Both these methods are reported to give inseparable mixtures of diastereomeric furanone products.

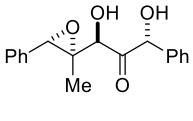
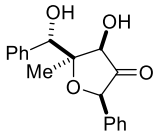
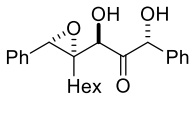
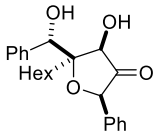
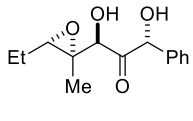
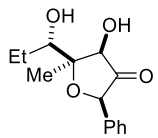
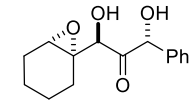
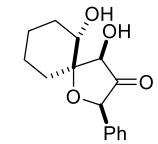
We envisioned an acid-mediated cyclization of the epoxy-keto-diols in Table 7 as a route to fully substituted tetrahydrofuran-3-one cores with high dr. Treatment of the epoxy-keto-diol **5k** with $BF_3 \cdot OEt_2$ at rt promoted cyclization to the dihydroxy-tetrahydrofuran-3-one **6k** as a single diastereomer in 90% isolated yield. Compound **6k** is exclusively formed via a 5-exo tet cyclization that involves attack of the benzylic alcohol at the congested 3^o carbon of the epoxide. Under acid catalysis, it is known that epoxides open via attack of nucleophiles at the more substituted carbon atom, and the 5-exo mode of cyclization is favored due to the low ring strain of the tetrahydrofuranyl alcohol products. The stereochemistry and regioselectivity of the cyclization were confirmed by X-ray structure determination of **6k** (entry 1, Table 6). The structure exhibits a five membered tetrahydrofuran-3-one core with inversion at the tertiary carbon center of the epoxide and an *anti*-relationship between the hydroxyl groups (Figure 1). The acid *p*-TsOH gave similar results (86% yield by ^1H NMR), although higher temperature and longer reaction times were required and minor side products were produced. An α-hexyl substrate performed equally well furnishing the dihydroxy-tetrahydrofuran-3-one **6m** in 92% yield under $BF_3 \cdot OEt_2$ mediated condition. Both $BF_3 \cdot OEt_2$ and *p*-TsOH conditions were employed in the synthesis of dihydroxy furan-3-ones **6o** and **6p**. In each case, the epoxy keto diols **5o** and **5p** were smoothly transformed into the dihydroxy-tetrahydrofuran-3-ones **6o** and **6p** in 77 and 65% yield, respectively (entry 3 and 4). Product **6p** is interesting in that it contains a spirocyclic ether unit that is found in a number of natural products, including theaspirone isolated from tea,[64] kuroyurinidine from the bulb of fritillaria maximowiczii[65] and numerous others. These oxaspirodecane derivatives exhibit biological activity, as exemplified by muscarinic

cholinomimetics.[66] It is reported that synthesis of oxaspirodecane systems suffer from tedious and low-yielding synthetic methods.[66, 67] Our approach for the diastereoselective synthesis of dihydroxy-tetrafuran-3-ones thus adds to the synthetic repertoire to access these challenging structural motifs.[39]

Table 7: Synthesis of Fully Substituted Dihydroxy-tetrahydrofuran-3-ones from Epoxy-keto-diols.

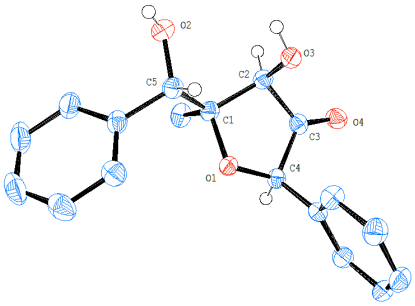


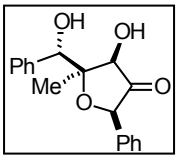
5 **6**

entry	epoxide-1,3-ketodiol	furanone		dr	yield (%)[a]
1.			**6k**	>20:1	90[b]
2.			**6m**	>20:1	91[b]
3.			**6o**	>20:1	77[c]
4.			**6p**	>20:1	65[c]

[a.] Isolated yield; [b.] $BF_3{\cdot}OEt_2$ used. [c.] *p*-TsOH in THF/H_2O.

Figure 1: ORTEP of Dihydroxy-hydrofuran-3-one 6k Illustrating the *anti* -Relationship of the Hydroxyl Groups.





3. Conclusion:

Chemoselectivity has been called the most challenging problem facing synthetic organic chemists.[68] In the oxidation of vinyl boronate esters with peroxides under basic condition, it is well known that oxidation occurs preferentially at the B–C bond rather than the C=C bond.[1] We have developed a method to reverse the chemoselectivity. The resulting products are synthetically useful, opening a new manifold of chemistry for vinyl boronate esters.

Outlined herein is the one-pot synthesis of a variety of 2-B(pin)-substituted allylic and bis-allylic alcohols using readily generated 1-alkenyl-1,1-heterobimetallics. Highly chemo- and diastereoselective oxidation of 2-B(pin)-substituted allylic alcohols and bis-allylic alcohols afforded B(pin)-substituted epoxy alcohols and bis-epoxy alcohols respectively, with the latter containing five contiguous stereocenters. The epoxidations were catalyzed by $OV(acac)_2$ and proceeded under neutral conditions with excellent diastereoselectivity (dr >20:1) and good to excellent yields.

We have also investigated the relative rate of epoxidation of the two double bonds in B(pin)-substituted bis-allylic alcohols. By variation of the electronics of the two vinyl groups, each can be selectively epoxidized. To the best of our knowledge, this is the first study to probe the relative reactivity of vinyl B(pin) vs. alkyl substituted vinyls in epoxidation reactions.

We have also demonstrated that the B(pin)-substituted epoxy alcohols are useful synthetic intermediates. Previously, vinyl boronate esters were precursors to ketones and 2-B(pin)-substituted allylic alcohols to a-hydroxy ketones. Employing the tandem diastereoselective C=C epoxidation/B–C bond oxidation, vinylboronate esters can now serve as precursors to α,α′-dihydroxy ketone motifs. Thus, 2-B(pin)-substituted allylic and bis-allylic alcohols could be transformed into 2-keto-*anti*-1,3-diols and epoxy-2-keto-*anti*-1,3-diols, respectively, after diastereoselective C=C epoxidation/B–C bond oxidations. Given the common place of such polyoxygenated hydrocarbons in natural products, we anticipate that these methods will be useful. Finally, we report a facile acid-mediated ring-opening of epoxide-substituted 2-keto-*anti*-1,3-diols to provide access to fully substituted dihydroxy-tetrahydrofuran-3-ones as single diastereomers. The methods introduced herein provide access to a variety of polyoxygenated compounds that would be difficult to efficiently prepare by other methods.

Acknowledgements: I want to thank Dr. Mahmud Hussain for his great contribution in this project. After his work on bimetallic addition to aldehydes, he initiated this bimetallic addition to α, β-unsaturated aldehydes project. I took over the project after his

graduation. I also want to thank Dr. Osvaldo Gutierrez for performing preliminary calculations.

4. Experimental Section:

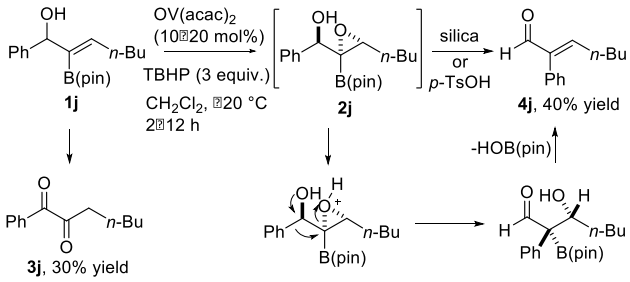
General Methods. All reactions were performed under a nitrogen atmosphere with oven-dried glassware. All manipulations involving dicyclohexylborane and dimethylzinc were carried out under an inert atmosphere in a Vacuum Atmospheres drybox with an attached MO-40 Dritrain or by using standard Schlenk or vacuum line techniques. Chemicals were obtained from Aldrich, Acros, or Strem Chemicals unless otherwise specified. The oxidant *tert*-butylhydroperoxide (TBHP) was purchased from Aldrich as a ~5.5 M anhydrous solution in decane and hydrogen peroxide from Fischer as a 30% aqueous solution. Solvents were purchased from Fischer Scientific. Toluene and dichloromethane were dried through activated alumina columns. Tetrahydrofuran was distilled from sodium and benzophenone under N_2. Liquid substrates were distilled prior to use. B(pin)-substituted alkynes were prepared by literature methods.[12, 14, 16, 21, 69-73] Neat dimethylzinc was obtained from Akzo Nobel from which 2.0 M solutions in toluene were prepared and stored in a Vacuum Atmospheres drybox. NMR spectra were obtained on Brüker 300, 360, 400 or 500 MHz Fourier transform spectrometers at the University of Pennsylvania NMR facility. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were referenced to residual solvent. $^{11}B\{^{1}H\}$ NMR spectra were referenced to $BF_3 \cdot OEt_2$. The infrared spectra were obtained using a Perkin-Elmer 1600 series spectrometer. HRMS data was obtained on a Waters LC-TOF mass spectrometer (model LCT-XE Premier) using

electrospray ionization in positive or negative mode, depending on analyte. Melting points were determined on a Uni-melt Thomas Hoover melting point apparatus and are uncorrected. Thin-layer chromatography was performed on Whatman precoated silica gel 60 F-254 plates and visualized by ultraviolet light or by staining with ceric ammonium molybdate, phosphomolybdic acid or potassium permanganate solutions. Silica gel (Silicaflash, P60, 40-63 μm, Silicycle) was used for airflashed chromatography, and deactivated silica gel was prepared by addition of 15 mL of Et_3N to 1 L of silica gel. Full characterizations of compounds **1a**–**1j**, **2b**–**2h**, **2j**, **3j**, **4j** and **5a**–**5i** were reported in our preliminary communication.[12]

Caution. *Dialkylzinc reagents are pyrophoric. Care must be used when handling them.*

Optimization of the epoxidation of the benzylic substrate **1j** proved to be more challenging. The epoxide **2j** was observed by TLC along with the diketone **3j** (Scheme S1). Purification of the reaction mixture on silica gel resulted in decomposition of the B(pin)-substituted epoxide with formation of the a,b-unsaturated aldehyde **4j** in ~40% yield (entries 12–13 in Table S2, and Scheme S1). We hypothesized that the enal **4j** arose via an acid or Lewis acid promoted semi-pinacol rearrangement followed by *syn*-elimination of the HO–B(pin). A similar HO–BAr_2 elimination takes place in the boron Wittig-type reaction.[74, 75] The elimination mechanism in Scheme S1 is consistent with the observed double bond geometry in the enal **4j**. The byproduct **3j** was identified as the known diketone.[76] Vanadium(V) catalysts are known to oxidize alcohols to the corresponding ketones in the presence of TBHP.[77, 78] Diketone **3j** may be formed by

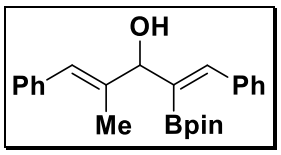
initial oxidation of the benzylic alcohol to the ketone followed by oxidation of the vinyl boronate ester to form the dione.



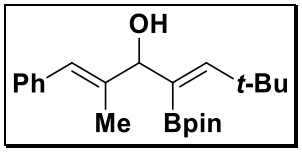
Scheme S1: Key Intermediates in the Proposed Mechanism of the Epoxy Alcohol Rearrangement to form Enal **4j**

General Procedure A: Synthesis of B(pin)-substituted Bis-allylic Alcohols. To a suspension of $HBCy_2$ (1.2 equiv) in toluene (2.0 mL) under N_2 was added alkyne-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (1.2 equiv) and the reaction mixture was stirred for 30 min at rt, after which it was homogeneous. The reaction vessel was cooled to –78 °C and treated with Me_2Zn (1.2 equiv, 2.0 M in toluene) for 30–45 min. The solution was then warmed to –10 °C and the enal (1 equiv) was added. The reaction mixture was stirred at –15 °C until TLC showed complete consumption of the aldehyde (8–12 h). The reaction mixture was then diluted with EtOAc and quenched with saturated NH_4Cl at 0 °C. The organic layer was separated and the aqueous solution was extracted three times with 10 mL of EtOAc. The combined organic solution was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel. The bis-allylic alcohol products are susceptible to oxidation of the B–C bond on silica under air. Rapid purification is therefore necessary

to minimize oxidation to the ketones, which elute at similar R_f values to the bis-allylic alcohols. The bis-allylic alcohols are stored under N_2 at 0 °C to preserve their purity.

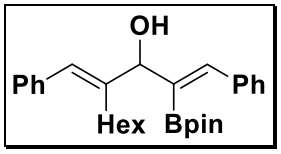


(1*E*,4*E*)-2-Methyl-1,5-diphenyl-4(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)penta-1,4-dien-3-ol (1k). The product was prepared by General Procedure A using *α*-methyl cinnamaldehyde (0.42 mL, 3.0 mmol) and 4,4,5,5-tetramethyl-2-(phenylethynyl)-1,3,2-dioxaborolane (0.82 g, 3.6 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 90:10) to afford the bis-allylic alcohol **1k** (1.04 g, 92% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.1 Hz, 2H), 7.38 – 7.20 (m, 8H), 7.18 (s, 1H), 6.71 (s, 1H), 4.86 (d, *J* = 4.5 Hz, 1H), 2.65 (d, *J* = 5.7 Hz, 1H), 1.90 (s, 3H), 1.24 (s, 12H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 141.0, 139.2, 137.9, 137.7, 129.0, 128.3, 128.0, 127.9, 127.6, 126.2, 125.2, 83.9, 81.9, 24.9, 24.7, 14.8 (the quaternary vinyl C bearing the boron is not observed); ^{11}B{^{1}H} NMR ($CDCl_3$,128 MHz) δ 30.5; IR (neat) 3448, 3058, 3026, 2930, 2855, 1684, 1625, 1600, 1494, 1449, 1312, 1248, 1143 cm^{-1}; HRMS *m/z* 399.2118 [$(M+Na)^+$; calcd for $C_{24}H_{29}BO_3Na$: 399.2107].



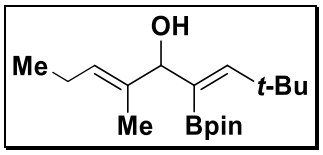
(1*E*,4*E*)-2,6,6-Trimethyl-1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-1,4-dien-3-ol (1l). The product was prepared by General Procedure A using *α*-methyl cinnamaldehyde (0.28 mL, 2.0 mmol) and 2-(3,3-

dimethylbut-1-ynl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.55 g, 2.4 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 90:10) to afford the bis-allylic alcohol **1l** (0.60 g, 84% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 4H), 7.23 – 7.17 (m, 1H), 6.66 (s, 1H), 6.14 (s, 1H), 4.54 (d, *J* = 5.4 Hz, 1H), 2.55 (d, *J* = 6.3 Hz, 1H), 1.79 (s, 3H), 1.25 (s, 6H), 1.24 (s, 6H), 1.14 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 154.1, 139.9, 138.3, 129.3, 128.2, 126.3, 124.1, 84.0, 83.4, 34.3, 30.5, 25.4, 25.3, 15.5 (the quaternary vinyl C bearing the boron is not observed); ^{11}B{^{1}H} NMR ($CDCl_3$,128 MHz) δ 30.0; IR (neat) 3469, 3023, 2978, 2954, 1640, 1600, 1480, 1380, 1304, 1253, 1142 cm^{-1}; HRMS *m/z* 379.2425 [$(M+Na)^+$; calcd for $C_{22}H_{33}BO_3Na$: 379.2420].

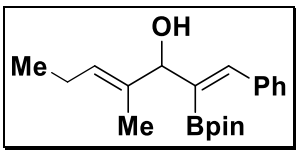


(1*E*,4*E*)-4-Benzylidene-1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dec-1-en-3-ol (1m). The product was prepared by General Procedure A using *α*-hexyl cinnamaldehyde (0.46 mL, 2.0 mmol) and 4,4,5,5-tetramethyl-2-(phenylethynyl)-1,3,2-dioxaborolane (0.55 g, 2.4 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 90:10) to afford the bis-allylic alcohol **1m** (0.54 g, 60% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.39 (m, 2H), 7.33 – 7.26 (m, 7H), 7.23 – 7.20 (m, 1H), 7.18 (s, 1H), 6.69 (s, 1H), 4.91 (s, 1H), 2.74 (s, 1H), 2.53 – 2.38 (m, 1H), 2.24 – 2.14 (m, 1H), 1.54 (p, *J* = 7.3 Hz, 2H), 1.31 – 1.21 (m, 18H), 0.86 (t, *J* = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 144.4, 141.8, 138.2, 138.1, 128.9, 128.7, 128.2, 128.1, 127.9, 126.5, 125.4, 84.1, 80.5, 31.7,

29.7, 29.0, 28.8, 25.2, 24.9, 22.8, 14.3 (the quaternary vinyl C bearing the boron is not observed); $^{11}B\{^{1}H\}$ NMR ($CDCl_3$,128 MHz) δ 30.3; IR (neat) 3423, 3057, 3025, 2928, 2856, 1685, 1625, 1600, 1493, 1450, 1379, 1310, 1249, 1142 cm^{-1}; HRMS *m/z* 469.2896 [$(M+Na)^+$; calcd for $C_{29}H_{39}BO_3Na$: 469.2890].

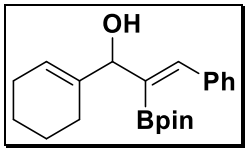


(3*E*,6*E*)-2,2,6-Trimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nona-3,6-dien-5-ol (1n). The product was prepared by General Procedure A using (*E*)-2-methylpent-2-enal (0.23 mL, 2.0 mmol) and 2-(3,3-dimethylbut-1-ynl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.55 g, 2.4 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 90:10) to afford the bis-allylic alcohol **1n** (0.41 g, 67% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (s, 1H), 5.51 – 5.40 (m, 1H), 4.37 (s, 1H), 2.33 (s, 1H), 2.01 (p, *J* = 7.6 Hz, 2H), 1.49 (s, 3H), 1.23 (s, 6H), 1.22 (s, 6H), 1.07 (s, 9H), 0.95 (t, *J* = 7.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 152.5, 136.0, 126.6, 83.7, 82.5, 82.4, 34.0, 30.5, 25.2, 21.1, 14.2, 13.0 (the quaternary vinyl C bearing the boron is not observed); $^{11}B\{^{1}H\}$ NMR ($CDCl_3$,128 MHz) δ 37.0; IR (neat) 3479, 2958, 2872, 1640, 1480, 1463, 1380, 1301, 1253, 1144 cm^{-1}; HRMS *m/z* 331.2419 [$(M+Na)^+$; calcd for $C_{18}H_{33}BO_3Na$: 331.2420].



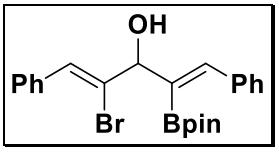
(1*E*,4*E*)-4-Methyl-1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-1,4-dien-3-ol (1o). The product was prepared by General

Procedure A using (*E*)-2-methylpent-2-enal (0.23 mL, 2.0 mmol) and 4,4,5,5-tetramethyl-2-(phenylethynyl)-1,3,2-dioxaborolane (0.55 g, 2.4 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 90:10) to afford the bis-allylic alcohol **1o** (0.37 g, 56% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.7 Hz, 2H), 7.33 – 7.17 (m, 3H), 7.09 (s, 1H), 5.56 (t, *J* = 6.9 Hz, 1H), 4.71 (s, 1H), 2.42 (s, 1H), 2.08 (p, *J* = 7.2 Hz, 2H), 1.64 (s, 3H), 1.24 (s, 12H), 1.00 (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 140.1, 138.3, 135.8, 128.5, 128.12 128.1, 127.6, 84.0, 81.4, 25.0, 24.9, 21.2, 14.2, 12.8 (the quaternary vinyl C bearing the boron is not observed); ^{11}B{^{1}H} NMR ($CDCl_3$,128 MHz) δ 30.0; IR (neat) 3433, 3027, 2930, 2977, 2873, 1629, 1600, 1494, 1449, 1380, 1310, 1247, 1143 cm^{-1}; HRMS *m/z* 351.2119 [(M+Na)$^{+}$; calcd for $C_{20}H_{29}BO_3Na$: 351.2107].

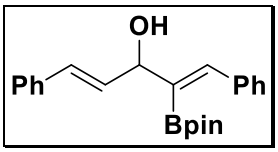


(*E*)-1-Cyclohexenyl-3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-en-1-ol (1p). The product was prepared by General Procedure A using cyclohex-1-enecarbaldehyde (0.23 mL, 2.0 mmol) and 4,4,5,5-tetramethyl-2-(phenylethynyl)-1,3,2-dioxaborolane (0.55 g, 2.4 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 90:10) to afford the bis-allylic alcohol **1p** (0.48 g, 71% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.2 Hz, 2H), 7.28 (t, *J* = 7.1 Hz, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.08 (s, 1H), 5.84 – 5.78 (m, 1H), 4.65 (s, 1H), 2.47 (s, 1H), 2.10 – 1.96 (m, 4H), 1.69 – 1.52 (m, 4H), 1.25 (s, 12H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 140.3, 139.3, 138.2, 128.5,

128.1, 127.6, 122.8, 84.0, 80.7, 25.2, 25.1, 25.0, 24.9, 22.8, 22.7 (the quaternary vinyl C bearing the boron is not observed); $^{11}B\{^{1}H\}$ NMR ($CDCl_3$,128 MHz) δ 30.3; IR (neat) 3423, 3026, 2978, 2927, 2856, 1626, 1600, 1495, 1449, 1389, 1309, 1248, 1142 cm^{-1}; HRMS *m/z* 363.2103 $[(M+Na)^+$; calcd for $C_{21}H_{29}BO_3Na$: 363.2107].



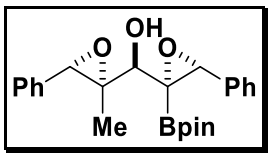
(1*Z*,4*E*)-2-Bromo-1,5-diphenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-1,4-dien-3-ol (1q). The product was prepared by General Procedure A using α-bromo cinnamaldehyde (0.42 mL, 2.0 mmol) and 4,4,5,5-tetramethyl-2-(phenylethynyl)-1,3,2-dioxaborolane (0.55 g, 2.4 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 90:10) to afford the bis-allylic alcohol **1q** (0.81 g, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.7 Hz, 2H), 7.43 (d, *J* = 7.6 Hz, 2H), 7.39 – 7.18 (m, 8H), 5.03 (d, *J* = 7.0 Hz, 1H), 3.19 (d, *J* = 8.1 Hz, 1H), 1.22 (s, 12H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 144.1, 137.6, 135.5, 129.3, 128.9, 128.8, 128.3, 128.2, 128.2, 128.1, 128.1, 84.3, 82.2, 25.1, 24.9 (the quaternary vinyl C bearing the boron is not observed); $^{11}B\{^{1}H\}$ NMR ($CDCl_3$,128 MHz) δ 30.2; IR (neat) 3433, 3025, 2979, 2930, 2874, 1627, 1600, 1493, 1447, 1391, 1313, 1249, 1141 cm^{-1}; HRMS *m/z* 463.1042 $[(M+Na)^+$; calcd for $C_{23}H_{26}BBrO_3Na$: 463.1056].



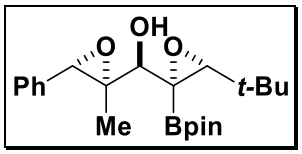
(1*E*,4*E*)-1,5-Diphenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-1,4-dien-3-ol (1r). The product was prepared by General Procedure A using cinnamaldehyde (0.13 mL, 1.0 mmol) and 4,4,5,5-tetramethyl-2-(phenylethynyl)-1,3,2-dioxaborolane (0.27 g, 1.2 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 90:10) to afford the bis-allylic alcohol **1r** (0.33 g, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 - 7.36 (m, 4H), 7.36 - 7.22 (m, 6H), 7.17 (s, 1H), 6.66 (d, J = 16 Hz, 1H), 6.39 (dd, *J* = 16.8, 5.8 Hz, 1H), 4.99 (s, 1H), 2.67 (s, 1H), 1.25 (s, 6H), 1.25 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 141.7, 137.9, 137.0, 131.7, 130.5, 128.7, 128.7, 128.1, 128.0, 127.7, 126.7, 84.2, 78.5, 35.7, 25.1, 24.8 (the quaternary vinyl C bearing the boron is not observed).

General Procedure B: Synthesis of B(pin)-substituted Bis-epoxides. To a Schlenk flask containing the B(pin)-substituted bis-allylic alcohol (1.0 equiv) was added 1 mL of freshly distilled CH_2Cl_2 followed by solid $OV(acac)_2$ (10 mol %) under N_2. The resulting greenish-blue solution was cooled to 0 ºC and a solution of TBHP (0.7–3.0 equiv, ~5.5 M solution in decane) in 1 mL of CH_2Cl_2 was added slowly to the reaction mixture over 10 min using a syringe pump at that temperature. The solution rapidly changed color to a dark brown. The reaction mixture was stirred at 0 ºC until TLC showed complete consumption of the bis-allylic alcohol (30 min –2 h). The crude reaction mixture was filtered through a short pad of silica, and the solvent was removed under reduced pressure (>90% purity by ^{1}H NMR). The crude product was further purified by flash column

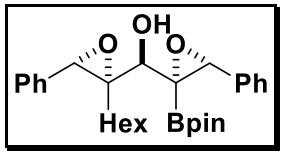
chromatography on silica gel. The epoxy boronate ester is susceptible to oxidation of the B–C bond on silica under air, and hence a rapid purification is necessary to minimize oxidation to the corresponding diol and other side products.



(2-Methyl-3-phenyloxiran-2-yl)(3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methanol (2k). The product was prepared by General Procedure B using bis-allylic alcohol **1k** (0.07 mmol, 1 equiv) and a solution of TBHP in 1 mL of CH_2Cl_2 (38.2 μL, ~5.5 M solution in decane, 3 equiv). The TBHP solution was added slowly to the reaction mixture over 10 min using a syringe pump. The crude reaction mixture was filtered through a short pad of silica to afford the epoxide (>90% purity by ^{1}H NMR). The product was further purified by flash column chromatography on silica gel (hexanes:EtOAc = 90:10) to afford a single diastereomer of the bis-epoxide **2k** (19.7 mg, 69% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 2H), 7.32 – 7.27 (m, 2H), 7.26 – 7.22 (m, 1H), 4.02 (s, 1H), 3.50 (d, J = 3.1 Hz, 1H), 3.38 (s, 1H), 2.72 (s, 1H), 2.14 – 2.06 (m, 1H), 1.97 – 1.82 (m, 3H), 1.51 – 1.39 (m, 2H), 1.35 – 1.25 (m, 2H), 1.00 (s, 6H), 0.93 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 136.0, 135.7. 128.2, 128.1, 128.0, 127.7, 126.9, 126.5, 84.8, 80.1, 65.2, 61.2, 60.1, 24.9, 24.6, 13.9 (the quaternary vinyl C bearing the boron is not observed); ^{11}B{^{1}H} NMR ($CDCl_3$,128 MHz) δ 29.7; IR (neat) 3521, 3032, 2979, 2931, 1605, 1498, 1454, 1381, 1335, 1250, 1134 cm^{-1}; HRMS *m/z* 431.1975 [$(M+Na)^+$; calcd for $C_{20}H_{29}BO_4Na$: 431.2007].

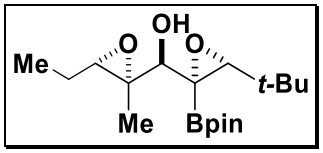


(3-*tert*-Butyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)(2-methyl-3-phenyloxiran-2-yl)methanol (2l). The product was prepared by General Procedure B using bis-allylic alcohol **1l** (0.10 mmol, 1 equiv) and a solution of TBHP in 1 mL of CH_2Cl_2 (54.5 μL, ~5.5 M solution in decane, 3 equiv). The TBHP solution was added slowly to the reaction mixture over 10 min using a syringe pump. The crude reaction mixture was filtered through a short pad of silica to afford the bis-epoxide (>90% purity by ^1H NMR). The product was further purified by flash column chromatography on silica gel (hexanes:EtOAc = 90:10) to afford a single diastereomer of the bis-epoxide **2l** (28.0 mg, 72% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.17 (m, 5H), 4.41 (s, 1H), 3.35 (s, 1H), 2.84 (s, 2H), 1.37 (s, 6H), 1.35 (s, 6H), 1.15 (s, 3H), 1.03 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 135.8, 128.1, 127.6, 126.8, 85.0, 80.8, 71.5, 65.1, 61.4, 31.7, 27.0, 25.8, 25.5, 13.9 (the quaternary vinyl C bearing the boron is not observed).



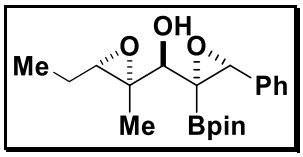
(2-Hexyl-3-phenyloxiran-2-yl)(3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxiran-2-yl)methanol (2m). The product was prepared by General Procedure B using bis-allylic alcohol **1m** (0.890 mmol, 1 equiv) and a solution of TBHP in 1 mL of CH_2Cl_2 (0.49 mL, ~5.5 M solution in decane, 3 equiv). The TBHP solution was added slowly to the reaction mixture over 10 min using a syringe pump.

The crude reaction mixture was filtered through a short pad of silica to afford the bis-epoxide (0.37 g, 86% ^{1}H NMR yield with internal standard CH_2Br_2, >90% purity by ^{1}H NMR). The product was further purified by flash column chromatography on silica gel (hexanes:EtOAc = 90:10) to afford a single diastereomer of the bis-epoxide **2m** (0.34 g, 80% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.4 Hz, 2H), 7.36 – 7.26 (m, 8H), 4.48 (s, 1H), 4.10 (s, 1H), 3.66 (d, *J* = 10.7 Hz, 1H), 2.96 (d, *J* = 10.8 Hz, 1H), 2.02 (ddd, *J* = 13.2, 10.4, 4.8 Hz, 1H), 1.21 – 1.14 (m, 1H), 1.13 – 1.07 (m, 2H), 1.06 – 0.97 (m, 10H), 0.96 (s, 6H), 0.76 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 136.0, 135.7, 128.1, 128.0, 128.0, 127.7, 126.9, 126.6, 84.8, 77.8, 68.0, 61.1, 61.0, 31.4, 29.3, 26.9, 24.8, 24.6, 22.5, 14.2 (the quaternary vinyl C bearing the boron is not observed); ^{11}B{^{1}H} NMR ($CDCl_3$,128 MHz) δ 28.4; IR (neat) 3521, 3032, 2979, 2931, 1605, 1498, 1454, 1418, 1381, 1335, 1250, 1134 cm^{-1}; HRMS *m/z* 431.1975 [(M+Na)$^+$; calcd for $C_{24}H_{29}BO_5Na$: 431.2006].



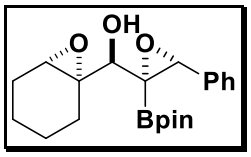
(3-(*tert*-Butyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxiran-2-yl)(3-ethyl-2-methyloxiran-2-yl)methanol (2n). The product was prepared by General Procedure B using bis-allylic alcohol **1n** (0.89 mmol, 1 equiv) and a solution of TBHP in 1 mL of CH_2Cl_2 (0.49 mL, ~5.5 M solution in decane, 3 equiv). The TBHP solution was added slowly to the reaction mixture over 10 min using a syringe pump. The crude reaction mixture was filtered through a short pad of silica to afford the bis-epoxide (0.27 g, 88% ^{1}H NMR yield with internal standard CH_2Br_2, >90% purity by ^{1}H

NMR). The product was further purified by flash column chromatography on silica gel (hexanes:EtOAc = 90:10) to afford a single diastereomer of the bis-epoxide **2n** (0.24 g, 80% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.24 (dd, *J* = 7.5, 5.1 Hz, 1H), 3.14 (s, 1H), 2.74 (s, 1H), 2.69 (s, 1H), 1.65 – 1.47 (m, 2H), 1.35 (s, 3H), 1.33 (s, 12H), 1.04 (t, *J* = 7.5 Hz, 3H), 0.99 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 84.8, 81.4, 72.0, 63.0, 62.3, 31.6, 27.0, 25.9, 25.5, 21.8, 14.3, 10.8 (the quaternary vinyl C bearing the boron is not observed); ^{11}B{^{1}H} NMR ($CDCl_3$,128 MHz) δ 30.0; IR (neat) 3525, 2977, 2933, 1411, 1381, 1334, 1250, 1135 cm^{-1}.



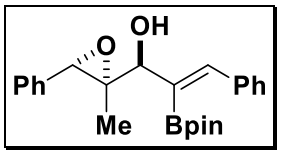
(3-Ethyl-2-methyl-2-methyloxiran-2-yl)(3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methanol (2o). The product was prepared by General Procedure B using bis-allylic alcohol **1o** (0.19 g, 0.59 mmol, 1 equiv) and a solution of TBHP in 1 mL of CH_2Cl_2 (0.32 mL, ~5.5 M solution in decane, 3 equiv). The TBHP solution was added slowly to the reaction mixture over 10 min using a syringe pump. The crude reaction mixture was filtered through a short pad of silica to afford the bis-epoxide (0.19 g, 90% ^{1}H NMR yield with internal standard CH_2Br_2, >90% purity by ^{1}H NMR). The product was further purified by flash column chromatography on silica gel (hexanes:EtOAc = 90:10) to afford a single diastereomer of the bis-epoxide **2o** (0.18 g, 84% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.39 (m, 2H), 7.33 – 7.25 (m, 3H), 4.02 (s, 1H), 3.35 (d, *J* = 10.1 Hz, 1H), 3.29 (dd, *J* = 7.2, 5.4 Hz, 1H), 2.78 (d, *J* = 10.3 Hz, 1H), 1.70 – 1.52 (m, 2H), 1.44 (s, 3H), 1.08 (t, *J* = 7.5 Hz, 3H), 1.01 (s, 6H), 0.93 (s,

6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 136.0, 128.1, 128.0, 126.6, 84.7, 80.4, 63.1, 62.2, 61.1, 24.9, 24.5, 21.8, 14.2, 10.7 (the quaternary vinyl C bearing the boron is not observed); $^{11}B\{^{1}H\}$ NMR ($CDCl_3$,128 MHz) δ 29.4; IR (neat) 3525, 2976, 2932, 1600, 1455, 1421, 1381, 1335, 1250, 1135 cm^{-1}; HRMS *m/z* 383.2007 $[(M+Na)^+$; calcd for $C_{20}H_{29}BO_5Na$: 383.2006].

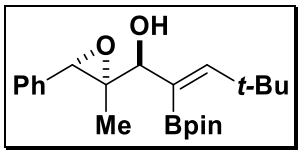


(7-Oxabicycloheptan-1-yl)(3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxiran-2-yl)methanol (2p). The product was prepared by General Procedure B using bis-allylic alcohol **1p** (0.12 g, 0.34 mmol, 1 equiv) and a solution of TBHP in 1 mL of CH_2Cl_2 (0.19 mL, ~5.5 M solution in decane, 3 equiv). The TBHP solution was added slowly to the reaction mixture over 10 min using a syringe pump. The crude reaction mixture was filtered through a short pad of silica to afford the bis-epoxide (0.10 g, 82% ^{1}H NMR yield with internal standard CH_2Br_2, >90% purity by ^{1}H NMR). The product was further purified by flash column chromatography on silica gel (hexanes:EtOAc = 90:10) to afford a single diastereomer of the bis-epoxide **2p** as white solid (92.4 mg, 73% yield). M.p 104-107 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 2H), 7.32 – 7.27 (m, 2H), 7.26 – 7.22 (m, 1H), 4.02 (s, 1H), 3.50 (d, *J* = 3.1 Hz, 1H), 3.38 (s, 1H), 2.72 (s, 1H), 2.14 – 2.06 (m, 1H), 1.97 – 1.82 (m, 3H), 1.51 – 1.39 (m, 2H), 1.35 – 1.25 (m, 2H), 1.00 (s, 6H), 0.93 (s, 6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 136.0, 128.1, 128.0, 126.5, 84.6, 80.1, 61.9, 60.9, 56.5, 25.6, 24.9, 24.6, 24.5, 20.1, 19.7 (the quaternary vinyl C bearing the boron is not observed); $^{11}B\{^{1}H\}$ NMR ($CDCl_3$,128

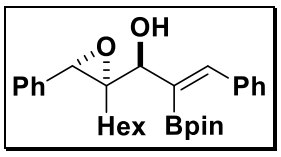
MHz) δ 29.7; IR (neat) 3529, 3062, 2978, 2936, 2860, 1605, 1498, 1450, 1421, 1381, 1336, 1249, 1132 cm^{-1}; HRMS *m/z* 395.2014 [$(M+Na)^+$; calcd for $C_{21}H_{29}BO_5Na$: 395.2006].



(*E*)-1-(2-Methyl-3-phenyloxiran-2-yl)-3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-en-1-ol (3k). The product was prepared by General Procedure B using bis-allylic alcohol **1k** (0.10 mmol, 1 equiv) and a solution of TBHP in 1 mL of CH_2Cl_2 (18.2 μL, ~5.5 M solution in decane, 1 equiv). The TBHP solution was added slowly to the reaction mixture over 30 min using a syringe pump. The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 90:10) to afford the mono-epoxide **3k** (27.1 mg, 69% yield). ^1H NMR (500 MHz, $CDCl_3$); δ 7.47 – 7.25 (m, 10H), 7.14 (s, 1H), 4.51 (s, 1H), 4.41 (s, 1H), 2.81 (s, 1H), 1.35 (s, 6H), 1.31 (s, 6H), 1.15 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 142.8, 138.0, 136.4, 128.7, 128.2, 128.2, 128.1, 127.5, 126.7, 84.2, 80.1, 65.7, 60.5, 25.2, 25.1, 14.3 (the quaternary vinyl C bearing the boron is not observed); $^{11}B\{^1H\}$ NMR ($CDCl_3$,128 MHz) δ 30.2; IR (neat) 3445, 3028, 2978, 2929, 2856, 1626, 1601, 1497, 1449, 1391, 1380, 1311, 1252, 1143 cm^{-1}.

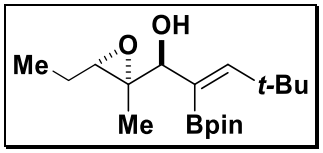


(*E*)-4,4-Dimethyl-1-(2-methyl-3-phenyloxiran-2-yl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-en-1-ol (3l). The product was prepared by General Procedure B using bis-allylic alcohol **1l** (0.1 mmol, 1 equiv) and a solution of TBHP in 1 mL of CH_2Cl_2 (14.6 μL, ~5.5 M solution in decane, 0.8 equiv). The TBHP solution was added slowly to the reaction mixture over 30 min using a syringe pump. The crude reaction mixture was filtered through a short pad of silica to afford the mono-epoxide (>90% purity by ^{1}H NMR). The product was further purified by flash column chromatography on silica gel (hexanes:EtOAc = 90:10) to afford the mono-epoxide **3l** (26.8 mg, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (m, 2H), 7.35 (t, J = 7.6 Hz, 2H), 7.30 – 7.28 (m, 1H), 6.08 (s, 1H), 4.35 (s, 1H), 4.29 (d, J = 2.7 Hz, 1H), 2.68 (d, J = 3.1 Hz, 1H), 1.36 (s, 6H), 1.35 (s, 6H), 1.12 (s, 9H), 1.06 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 154.4, 136.4, 127.8, 127.1, 126.5, 83.7, 80.6, 65.5, 60.0, 34.2, 30.1, 25.2, 25.0, 14.2 (the quaternary vinyl C bearing the boron is not observed); ^{11}B{^{1}H} NMR ($CDCl_3$,128 MHz) δ 30.5.



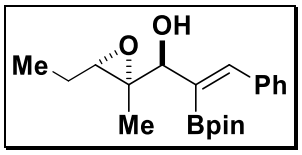
(*E*)-1-(2-Hexyl-3-phenyloxiran-2-yl)-3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-en-1-ol (3m). The product was prepared by General Procedure B using bis-allylic alcohol **1m** (0.35 mmol, 1 equiv) and a solution of TBHP in 1 mL of CH_2Cl_2 (51.0 μL, ~5.5 M solution in decane, 0.28 mmol, 0.8 equiv).

The TBHP solution was added slowly to the reaction mixture over 30 min using a syringe pump. The crude reaction mixture was filtered through a short pad of silica to afford the mono-epoxide (0.11 g, 86% ^{1}H NMR yield with internal standard CH_2Br_2, >90% purity by ^{1}H NMR). The product was further purified by flash column chromatography on silica gel (hexanes:EtOAc = 90:10) to afford the mono-epoxide **3m** (90.6 mg, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$); 7.46 – 7.27 (m, 10H), 7.15 (s, 1H), 4.67 (d, J = 3.9 Hz, 1H), 4.37 (s, 1H), 2.89 (d, J = 4.5 Hz, 1H), 1.50 – 1.44 (m, 2H), 1.35 (s, 6H), 1.31 (s, 6H), 1.25 – 1.06 (m, 8H), 0.82 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 143.1, 137.9, 136.4, 128.7, 128.2, 128.1, 128.0, 127.4, 126.7, 84.1, 77.7, 68.3, 60.7, 31.6, 29.6, 26.8, 25.1, 24.8, 22.6, 14.2 (the quaternary vinyl C bearing the boron is not observed); ^{11}B{^{1}H} NMR ($CDCl_3$,128 MHz) δ 30.1; IR (neat) 3470, 3027, 2977, 2955, 2929, 2858, 1626, 1602, 1496, 1455, 1391, 1310, 1250, 1143 cm^{-1}; HRMS *m/z* 485.2822 [(M+Na)$^+$; calcd for $C_{29}H_{39}BO_4Na$: 485.2839].



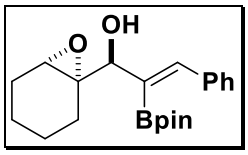
(*E*)-1-(3-Ethyl-2-methyloxiran-2-yl)-4,4--dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-en-1-ol (3n). The product was prepared by General Procedure B using bis-allylic alcohol **1n** (0.91 mmol, 1 equiv) and a solution of TBHP in 1 mL of CH_2Cl_2 (0.12 mL, ~5.5 M solution in decane, 0.7 equiv). The TBHP solution was added slowly to the reaction mixture over 30 min using a syringe pump. The crude reaction mixture was filtered through a short pad of silica to afford the mono-epoxide (0.15 g, 75% yield ^{1}H NMR yield with internal standard CH_2Br_2, >90% purity by

^{1}H NMR). The product was further purified by flash column chromatography on silica gel (hexanes:EtOAc = 90:10) to afford the mono-epoxide **3n** (0.13 g, 63% yield). ^{1}H NMR (500 MHz, $CDCl_3$); δ 6.02 (s, 1H), 4.09 (d, *J* = 3.3 Hz, 1H), 3.08 (dd, *J* = 7.4, 5.2 Hz, 1H), 2.52 (d, *J* = 3.4 Hz, 1H), 1.65 – 1.58 (m, 1H), 1.58 – 1.50 (m, 1H), 1.28 (s, 12H), 1.25 (s, 3H), 1.09 (s, 9H), 1.04 (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 154.6, 83.8, 81.4, 63.4, 61.5, 34.4, 30.4, 25.5, 25.2, 21.8, 14.9, 11.0 (the quaternary vinyl C bearing the boron is not observed); ^{11}B{^{1}H} NMR ($CDCl_3$,128 MHz) δ 30.2; IR (neat) 3480, 2969, 2875, 1639, 1464, 1411, 1373, 1305, 1255, 1144 cm^{-1}; HRMS *m/z* 347.2362 [(M+Na)$^+$; calcd for $C_{18}H_{33}BO_4Na$: 347.2370].

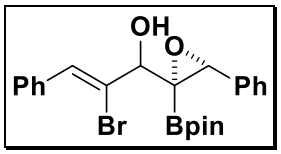


(*E*)-1-(3-Ethyl-2-methyloxiran-2-yl)-3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-en-1-ol (3o). The product was prepared by General Procedure B using bis-allylic alcohol **1o** (1.2 mmol, 1 equiv) and a solution of TBHP in 1 mL of CH_2Cl_2 (0.15 mL, ~5.5 M solution in decane, 0.7 equiv). The TBHP solution was added slowly to the reaction mixture over 30 min using a syringe pump. The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 90:10) to afford the mono-epoxide **3o** (0.16 g, 54% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ7.38 (d, *J* = 6.5 Hz, 2H), 7.32 – 7.23 (m, 3H), 7.07 (s, 1H), 4.33 (s, 1H), 3.13 (t, *J* = 6.3 Hz, 1H), 2.75 (s, 1H), 1.68 – 1.54 (m, 2H), 1.36 (s, 3H), 1.28 (s, 6H), 1.26 (s, 6H), 1.07 (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 142.9, 138.0, 128.6, 128.2, 128.0, 84.0, 80.6, 63.4, 61.6, 25.1, 24.9, 21.8, 14.7, 11.0 (the quaternary

vinyl C bearing the boron is not observed); $^{11}B\{^{1}H\}$ NMR ($CDCl_3$,128 MHz) δ 30.8; IR (neat) 3463, 3026, 2976, 2931, 2876, 1626, 1600, 1493, 1459, 1390, 1311, 1252, 1143 cm^{-1}; HRMS *m/z* 367.2054 [$(M+Na)^+$; calcd for $C_{20}H_{29}BO_4Na$: 367.2057].



(*E*)-1-(7-Oxabicycloheptan-1-yl)-3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-en-1-ol (3p). The product was prepared by General Procedure B using bis-allylic alcohol **1p** (0.07 mmol, 1 equiv) and a solution of TBHP in 1 mL of CH_2Cl_2 (9.5 μL, ~5.5 M solution in decane, 0.7 equiv). The TBHP solution was added slowly to the reaction mixture over 30 min using a syringe pump. The crude reaction mixture was filtered through a short pad of silica to afford the mono-epoxide (>90% purity by ^{1}H NMR). The product was further purified by flash column chromatography on silica gel (hexanes:EtOAc = 90:10) to afford the mono-epoxide **3p** (9.1 mg, 52% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ7.40 (d, *J* = 7.7 Hz, 2H), 7.33 – 7.22 (m, 3H), 7.08 (s, 1H), 4.31 (s, 1H), 3.40 – 3.26 (m, 1H), 2.70 (s, 1H), 2.04 – 1.81 (m, 4H), 1.51 – 1.40 (m, 2H), 1.36 – 1.22 (m, 14H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 143.3, 138.0, 128.7, 128.1, 128.0, 84.0, 80.2, 62.4, 56.4, 25.5, 25.2, 25.1, 24.5, 20.3, 20.0 (the quaternary vinyl C bearing the boron is not observed); $^{11}B\{^{1}H\}$ NMR ($CDCl_3$,128 MHz) δ 30.5; IR (neat) 3479, 3025, 2974, 2932, 2875, 1627, 1600, 1494, 1461, 1389, 1311, 1253, 1143cm^{-1}; HRMS *m/z* 379.2052 [$(M+Na)^+$; calcd for $C_{21}H_{29}BO_4Na$: 379.2057].

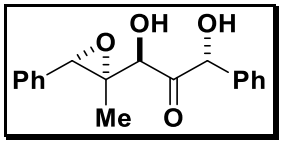


(*Z*)-2-Bromo-3-phenyl-1-(3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxiran-2-yl)prop-2-en-1-ol (4q). The product was prepared by General Procedure B using bis-allylic alcohol **1q** (0.14 g, 0.31 mmol, 1 equiv) and a solution of TBHP in 1 mL of CH_2Cl_2 (0.17 mL, ~5.5 M solution in decane, 3.0 equiv). The TBHP solution was added slowly to the reaction mixture over 30 min using a syringe pump. The crude reaction mixture was filtered through a short pad of silica to afford the mono-epoxide. The product was further purified by flash column chromatography on silica gel (hexanes:EtOAc = 90:10) to afford the mono-epoxide **4q** (87.9 mg, 62% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 – 7.61 (m, 2H), 7.50 – 7.45 (m, 2H), 7.41 – 7.36 (m, 3H), 7.35 – 7.30 (m, 3H), 7.21 (s, 1H), 4.33 (s, 2H), 3.20 (s, 1H), 0.98 (s, 6H), 0.96 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 135.80, 135.28, 130.47, 129.39, 128.41, 128.33, 128.16, 128.11, 126.50, 125.94, 85.01, 79.40, 61.30, 24.73, 24.67 (the quaternary vinyl C bearing the boron is not observed); IR (neat) 3454, 3061, 3030, 2979, 2930, 1605, 1495, 1447, 1373, 1261, 1110, 1029 cm^{-1}; HRMS *m/z* 479.0996 [(M+Na)$^+$; calcd for $C_{23}H_{26}BBrO_4Na$: 479.1005].

General Procedure D: Synthesis of Epoxy-2-keto-*anti*-1,3-diols. To a 20 mL vial was added B(pin)-substituted bis-epoxide and 1 mL THF. The solution was cooled at 0 °C and solid $NaBO_3 \cdot H_2O$ (3 equiv) was added followed by 1 mL of H_2O. The reaction mixture was stirred and allowed to warm to rt. Stirring was continued until TLC showed consumption of the bis-epoxide (4–6 h). The reaction mixture was then diluted with

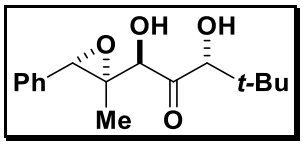
water (1 mL) and extracted with diethyl ether(3 x 10 mL). The combined organic layer was then washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexanes:EtOAc = 80:20).

General Procedure E: Synthesis of Epoxy-2-keto-*anti*-1,3-diols. To a 20 mL vial was added B(pin)-substituted bis-epoxide and 2 mL THF. The solution was cooled at 0 °C and 30 % H_2O_2 (3.3 equiv) and NaOH (1.1 equiv) were added to the solution. The reaction mixture was stirred and allowed to warm to rt. Stirring was continued until TLC showed consumption of the bis-epoxides (2–4 h). The reaction mixture was then diluted with water (1 mL) and extracted with diethyl ether (4 x 10 mL). The combined organic layer was then washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude was purified by flash chromatography on silica gel (hexanes:EtOAc = 80:20).

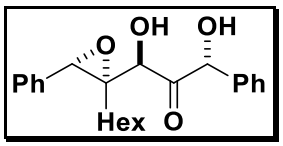


1,3-Dihydroxyl-1-(2-methyl-3-phenyloxiran-2-yl)-3-phenylpropan-2-one (5k). The product was prepared by General Procedure D using bis-epoxide **2k** (16.3 mg, 0.04 mmol) and $NaBO_3 \cdot H_2O$ (12.0 mg, 3 equiv, 0.12 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc =80:20) to afford the 1,3-ketodiol **5k** (9.3 mg, 78% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.45 (m, 2H), 7.43 – 7.28 (m, 8H), 5.80 (s, 1H), 4.13 (s, 1H),

4.02 (s, 1H), 3.97 (s, 1H), 3.51 (s, 1H), 0.98 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 209.7, 137.4, 134.5, 129.3, 129.1, 128.4, 128.3, 127.8, 126.7, 78.3, 77.8, 64.3, 63.1, 11.1; IR (neat) 3469, 3030, 2979, 2928, 2854, 1714, 1600, 1495, 1452, 1380, 1145 cm^{-1}; HRMS *m/z* 321.1108 [$(M+Na)^+$; calcd for $C_{18}H_{18}O_4Na$: 321.1103].

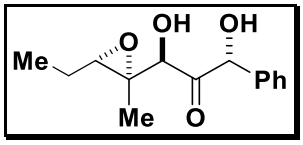


1,3-Dihydroxy-4,4-dimethyl-1-(2-methyl-3-phenyloxiran-2-yl)pentan-2-one (5l). The product was prepared by General Procedure D using bis-epoxide **2l** (23.7 mg, 0.06 mmol) and $NaBO_3 \cdot H_2O$ (18.0 mg, 3 equiv, 0.18 mmol). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc =80:20) to afford the 1,3-ketodiol **5l** (13.2 mg, 78% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.1 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 5.17 (s, 1H), 3.79 (s, 1H), 3.66 (s, 1H), 3.59 (s, 1H), 2.92 (s, 1H), 1.09 (s, 9H), 1.02 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 214.3, 139.0, 128.2, 128.1, 127.8, 85.1, 82.4, 76.8, 76.3, 35.2, 26.4, 18.8; IR (neat) 3427, 3062, 2979, 2928, 2855, 1712, 1600, 1480, 1409, 1380, 1304, 1144 cm^{-1}; HRMS *m/z* 301.1411 [$(M+Na)^+$; calcd for $C_{16}H_{22}O_4Na$: 301.1416].



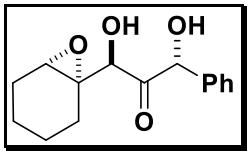
1-(2-Hexyl-3-phenyloxiran-2-yl)-1,3-dihydroxy-3-phenylpropan-2-one (5m). The product was prepared by General Procedure D using bis-epoxide **2m** (0.106 g, 0.22 mmol) and $NaBO_3 \cdot H_2O$ (65.9 mg, 3 equiv, 0.66 mmol).

The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc =80:20) to afford the 1,3-ketodiol **5m** (51.9 mg, 64% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.43 (m, 2H), 7.42 – 7.31 (m, 6H), 7.26 – 7.21 (m, 2H), 5.82 (s, 1H), 4.10 (s, 1H), 4.05 (s, 1H), 3.87 (s, 1H), 3.39 (s, 1H), 1.60 – 1.51 (m, 1H), 1.43 – 1.32 (m, 1H), 1.22 – 1.14 (m, 2H), 1.13 – 1.06 (m, 6H), 0.82 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 210.2, 137.7, 134.6, 129.3, 129.1, 128.4, 128.3, 127.8, 126.7, 77.8, 77.6, 65.7, 64.6, 31.4, 29.5, 25.4, 24.8, 22.6, 14.2; IR (neat) 3460, 3064, 3033, 2956, 2926, 2856, 1715, 1600, 1495, 1455, 1379, 1263, 1012 cm^{-1}; HRMS *m/z* 391.1888 [$(M+Na)^+$; calcd for $C_{23}H_{28}O_4Na$: 391.1885].



1-(3-Ethyl-2-methyloxiran-2-yl)-1,3-dihydroxy-3-phenylpropan-2-one (5o). The product was prepared by General Procedure E using bis-epoxide **2o** (80.0 mg, 0.22 mmol), NaOH (0.24 mmol, 1.1 equiv, 60 μL) and 30% H_2O_2 solution (0.73 mmol, 3.3 equiv, 22.5 μL). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc =80:20) to afford the 1,3-ketodiol **5o** (33.0 mg, 60% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 5H), 5.68 (d, *J* = 4.4 Hz, 1H), 4.13 (d, *J* = 6.2 Hz, 1H), 3.86 (d, *J* = 2.7 Hz, 1H), 3.34 (d, *J* = 3.8 Hz, 1H), 2.69 (t, *J* = 6.3 Hz, 1H), 1.62 – 1.47 (m, 2H), 1.15 (s, 3H), 1.02 (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ210.1, 137.5, 129.2, 128.9, 127.7, 78.8, 77.7, 65.1, 60.6, 21.9, 12.0, 10.5; IR (neat) 3460, 3064, 3033, 2955, 2926, 2856, 1715, 1603, 1495,

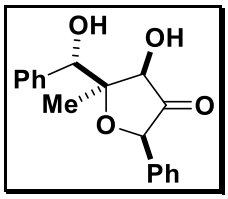
1455, 1379, 1263, 1012 cm^{-1}; HRMS *m/z* 273.1092 [$(M+Na)^+$; calcd for $C_{14}H_{18}O_4Na$: 273.1103].



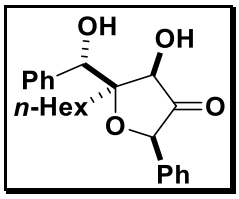
1-(7-Oxabicycloheptan-1-yl)-1,3-dihydroxy-3-phenylpropan-2-one (5p). The product was prepared by General Procedure E using bis-epoxide **2p** (70.8 mg, 0.27 mmol), NaOH (0.30 mmol, 1.1 equiv, 60 μL) and 30% H_2O_2 solution (0.89 mmol, 3.3 equiv, 27.4 μL). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc =80:20) to afford the 1,3-ketodiol **5p** (43.2 mg, 61% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.31 (m, 5H), 5.68 (d, *J* = 5.6 Hz, 1H), 4.10 (d, *J* = 6.6 Hz, 1H), 3.87 (d, *J* = 3.5 Hz, 1H), 3.34 (d, *J* = 4.5 Hz, 1H), 2.95 (d, *J* = 2.7 Hz, 1H), 1.98 – 1.83 (m, 1H), 1.78 – 1.69 (m, 1H), 1.49 – 1.40 (m, 2H), 1.40 – 1.32 (m, 2H), 1.29 – 1.22 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 209.8, 137.4, 129.2, 129.0, 127.8, 78.1, (one peak overlaps with the $CDCl_3$ peaks; two peaks are observed at 78.6, 78.0 in benzene-d_6) 60.0, 59.2, 24.6, 22.7, 20.1, 18.9; IR (neat) 3430, 2932, 2856, 1717, 1645, 1493, 1455, 1382, 1276, 1190, 1139 cm^{-1}; HRMS *m/z* 285.1100 [$(M+Na)^+$; calcd for $C_{15}H_{18}O_4Na$: 285.1103].

General Procedure F: Synthesis of Dihydroxy-dihydrofuran-3-(2*H*)-ones. In a 20 mL vial was added the epoxide-substituted keto-*anti*-1,3-diol (1 equiv, 0.05M) followed by dry THF, and the solution was cooled to 0 °C. Either neat $BF_3{\cdot}OEt_2$ or solid *p*-TsOH (1 equiv) was added slowly to the solution. The reaction mixture was allowed to warm to

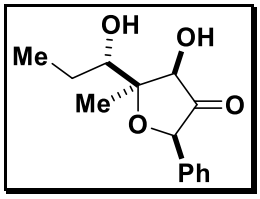
rt and stirred at rt until TLC showed consumption of the epoxy keto diol (2–3 h). The reaction mixture was then diluted with water (1 mL) and extracted with diethyl ether(4 x 10 mL). The combined organic layer was then washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude was purified by flash chromatography on silica gel (hexanes:EtOAc = 80:20).



4-Hydroxy-5-(hydroxyl(phenyl)methyl)-5-methyl-2-phenyldihydrofuran-3-(2*H*)-one (6k). The product was prepared by General Procedure F using epoxide keto diol **5k** (43.3 mg, 0.15 mmol) and $BF_3{\cdot}OEt_2$ (0.15 mmol, 19.0 μL). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc =80:20) to afford the 1,3-ketodiol **6k** (40.3 mg, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.51 (m, 2H), 7.51 – 7.47 (m, 2H), 7.45 – 7.32 (m, 6H), 5.26 (s, 1H), 5.02 (s, 1H), 4.05 (s, 1H), 3.96 (s, 1H), 3.07 (s, 1H), 1.18 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 211.4, 138.8, 136.2, 128.8, 128.7, 128.3, 128.3, 127.9, 127.0, 84.0, 79.9, 76.8, (one peak overlaps with the $CDCl_3$ peaks), 19.3; IR (neat) 3437, 3064, 3033, 2930, 1764, 1603, 1495, 1453, 1073, 1054, 1028 cm^{-1}; HRMS *m/z* 297.1136 [$(M-H)^-$; calcd for $C_{18}H_{17}O_4$: 297.1127].

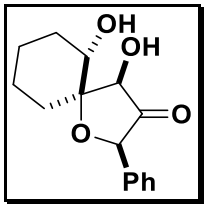


5-Hexyl-4-hydroxy-5-(hydroxyl(phenyl)methyl-2-phenyldihydrofuran-3-2(H)-one (6m). The product was prepared by General Procedure F using epoxide keto diol **5m** (70.0 mg, 0.19 mmol) and $BF_3{\cdot}OEt_2$ (0.19 mmol, 24.0 μL). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc =80:20) to afford the 1,3-ketodiol **6m** (63.7 mg, 91% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.53 (m, 2H), 7.51 – 7.46 (m, 2H), 7.45 – 7.39 (m, 2H), 7.39 – 7.30 (m, 4H), 5.22 (s, 1H), 5.00 (s, 1H), 4.79 (s, 1H), 4.10 (s, 1H), 3.45 (s, 1H), 1.49 – 1.37 (m, 2H), 1.37 – 1.12 (m, 8H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 211.0, 138.8, 136.4, 128.9, 128.7, 128.6, 128.4, 128.1, 127.1, 85.5, 80.0, 78.1, 76.1, 33.1, 31.8, 29.8, 22.9, 22.7, 14.2; IR (neat) 3401, 3064, 3033, 2954, 2929, 2857, 1764, 1602, 1495, 1453, 1055, 1027 cm^{-1}; HRMS *m/z* 367.1927 [(M-H)$^-$; calcd for $C_{23}H_{27}O_4$: 367.1909].



4-Hydroxy-5-(1-hydroxypropyl)-5-methyl-phenyldihydrofuran-3(2*H*)-one (6o). The product was prepared by General Procedure F using epoxide keto diol **5o** (25.0 mg, 0.10 mmol) and *p*-TsOH (0.10 mmol, 19.4 mg). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc =80:20) to afford the 1,3-ketodiol **6o** (19.3 mg, 77% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.45 (m,

2H), 7.42 – 7.36 (m, 2H), 7.37 – 7.29 (m, 1H), 5.12 (s, 1H), 4.13 (s, 1H), 3.91 (s, 1H), 3.76 (dd, *J* = 10.6, 2.3 Hz, 1H), 2.78 (s, 1H), 1.84 – 1.72 (m, 1H), 1.67 – 1.54 (m, 1H), 1.43 (s, 3H), 0.99 (t, *J* = 7.4 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 211.3, 136.3, 128.8, 128.5, 126.6, 83.5, 78.8, 78.6, 77.6, 24.0, 20.2, 11.1; IR (neat) 3370, 3064, 3033, 2966, 2931, 2873, 1764, 1603, 1495, 1452, 1054 cm^{-1}; HRMS *m/z* 273.1095 [$(M+Na)^+$; calcd for $C_{14}H_{18}O_4Na$: 273.1103].



4,6-Dihydroxy-2-phenyl-1-oxaspiro[4,5]decan-3-one (6p). The product was prepared by General Procedure F using epoxide keto diol **5p** (13.1 mg, 0.05 mmol) and *p*-TsOH (0.05 mmol, 9.7 mg). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc =80:20) to afford the 1,3-ketodiol **6p** (8.5 mg, 65% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.49 (m, 2H), 7.43 – 7.37 (m, 2H), 7.36 – 7.31 (m, 1H), 5.14 (s, 1H), 4.21 (s, 1H), 3.97 (dd, *J* = 8.9, 4.5 Hz, 1H), 3.73 (s, 1H), 2.50 (s, 1H), 2.07 – 1.93 (m, 2H), 1.88 – 1.76 (m, 3H), 1.74 – 1.66 (m, 1H), 1.63 – 1.54 (m, 1H), 1.48 – 1.39 (m, 1H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ211.4, 136.5, 128.8, 128.4, 126.3, 83.3, 78.4, 78.3, (quaternary C is missing or overlapping with the $CDCl_3$ peaks), 34.4, 30.6, 22.6, 22.4; IR (neat) 3402, 3065, 3033, 2934, 2863, 1767, 1603, 1495, 1455, 1157 cm^{-1}; HRMS *m/z* 261.1139 [[$(M-H)^-$; calcd for $C_{15}H_{17}O_4$: 261.1127].

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39. It should be noted that all stereochemical assignments of products are made by analogy to single crystal x-ray structures **2d, 3c, 3f,** and **6k**.

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Appendices

Appendix A1 NMR Spectra Relavant to Chapter 1

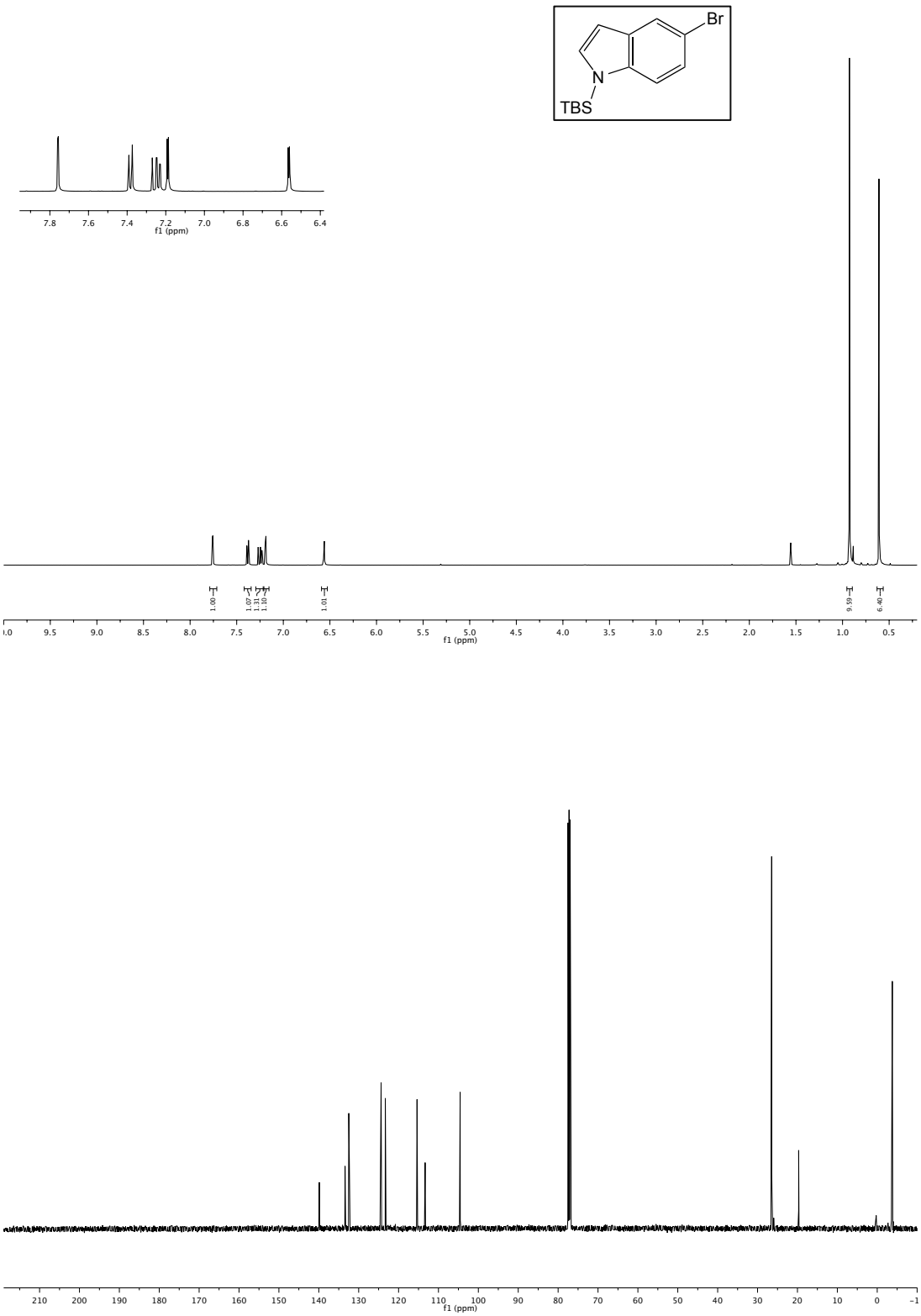


Figure S1 (**3j**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 5-bromo-1-(*tert*-butyldimethylsilyl)-1*H*-indole in $CDCl_3$.

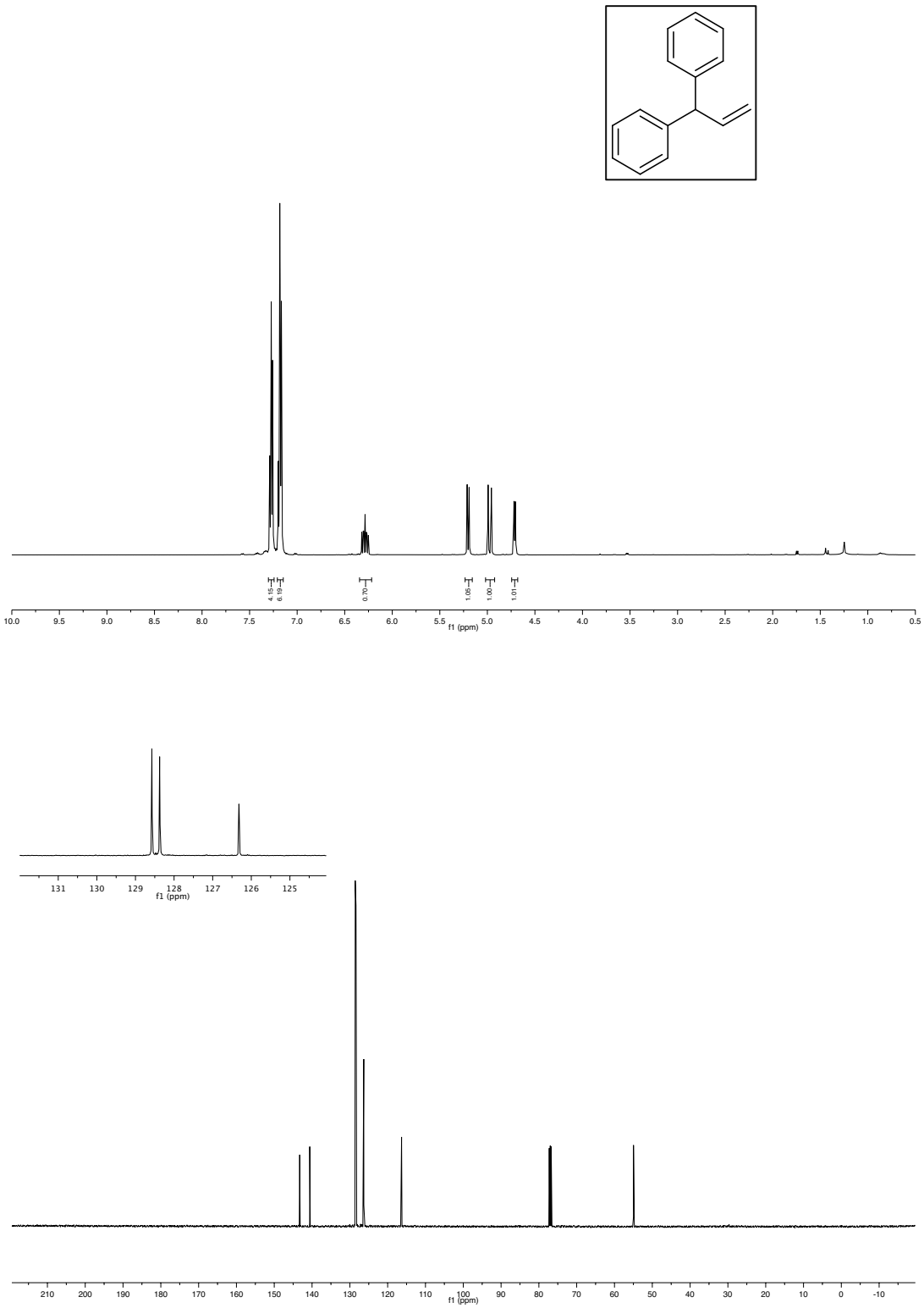


Figure S2 (**4a**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of prop-2ene-1,1-diyldibenzene in $CDCl_3$.

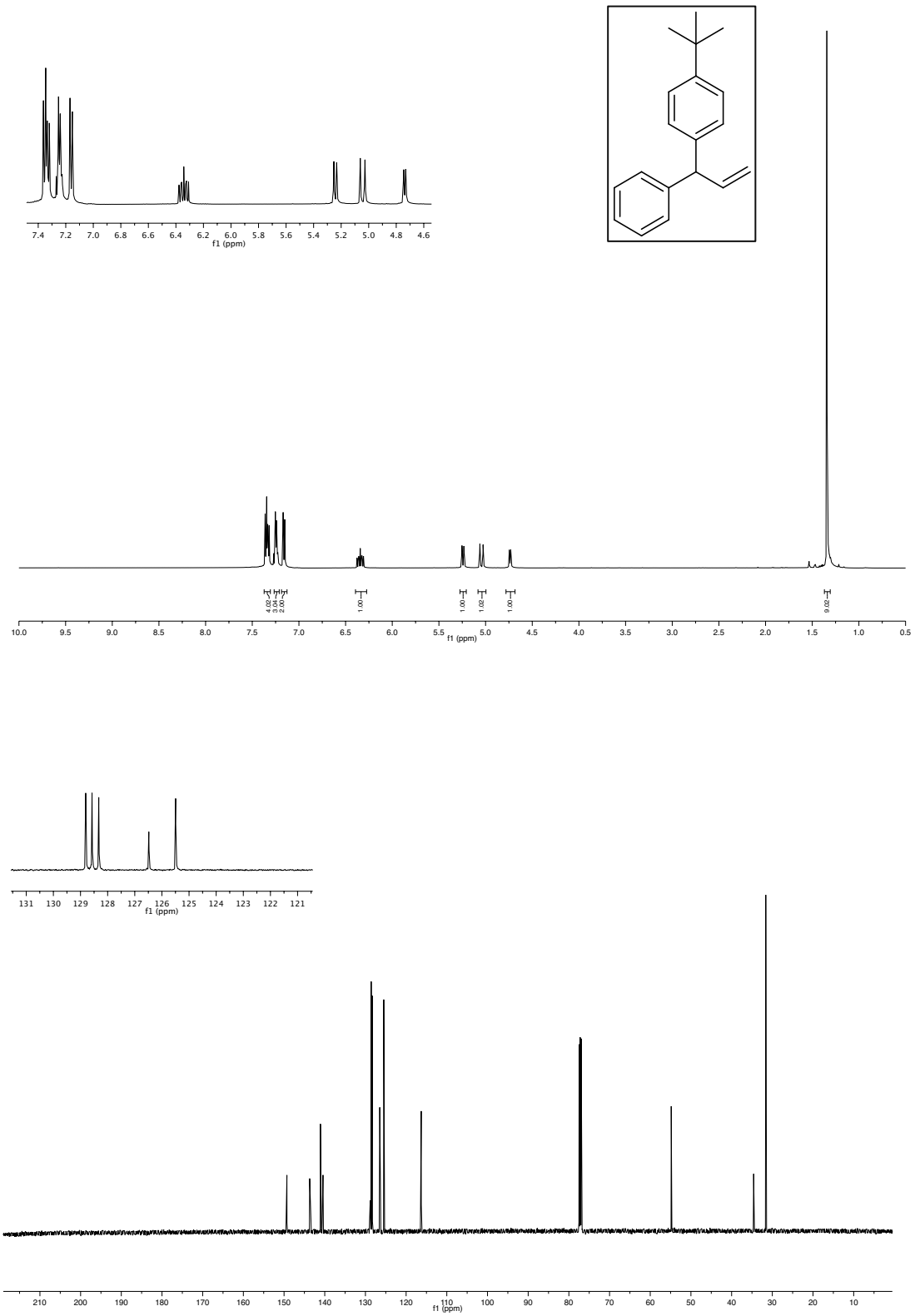


Figure S3 (**4b**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 1-(*tert*-butyl)-4-(1-phenylallyl)benzene in $CDCl_3$.

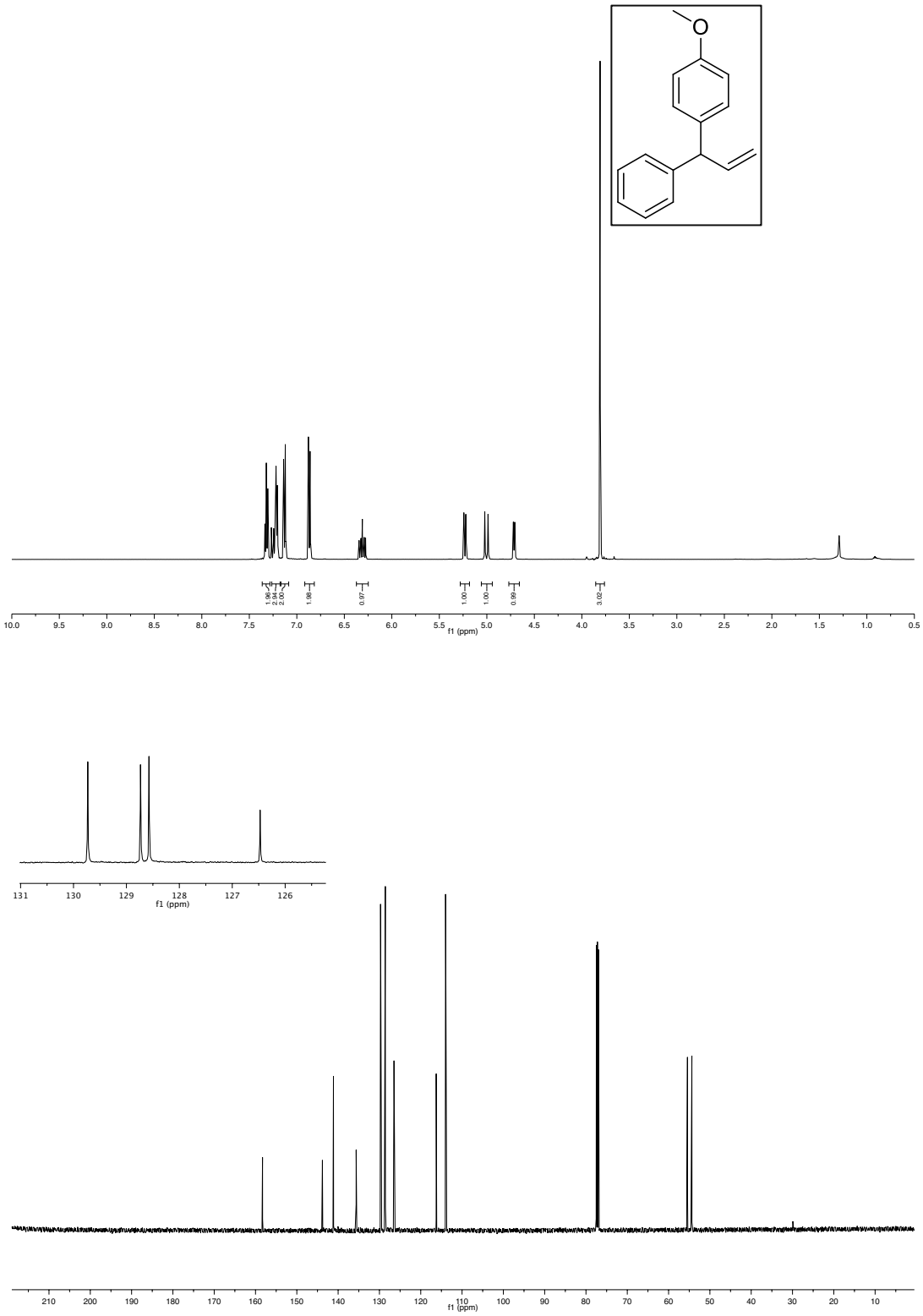


Figure S4 (**4c**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 1-methoxy-4-(1-phenylallyl)benzene in $CDCl_3$.

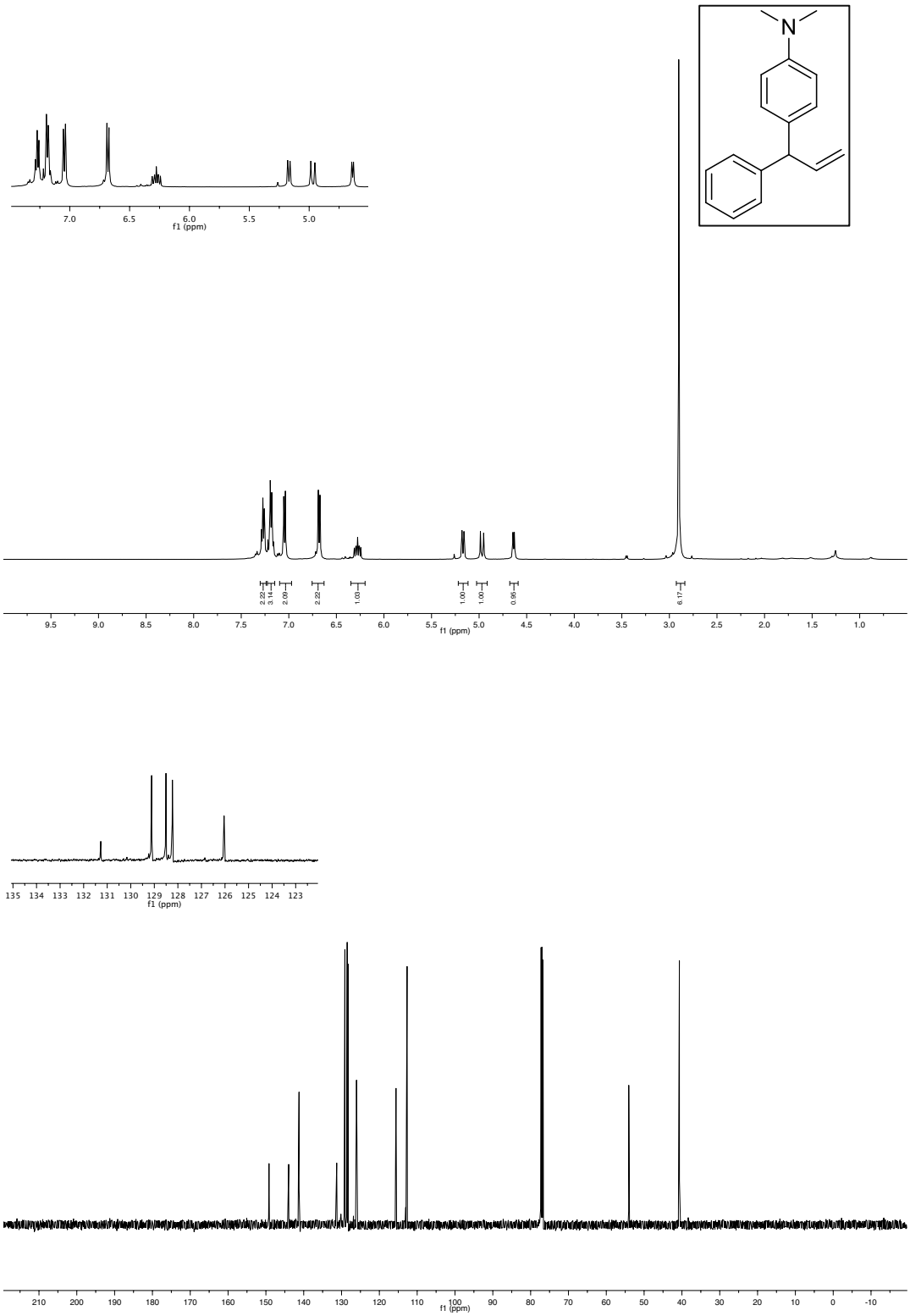


Figure S5 (**4d**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of N,N-dimethyl-4-(1-phenylallyl)aniline in $CDCl_3$.

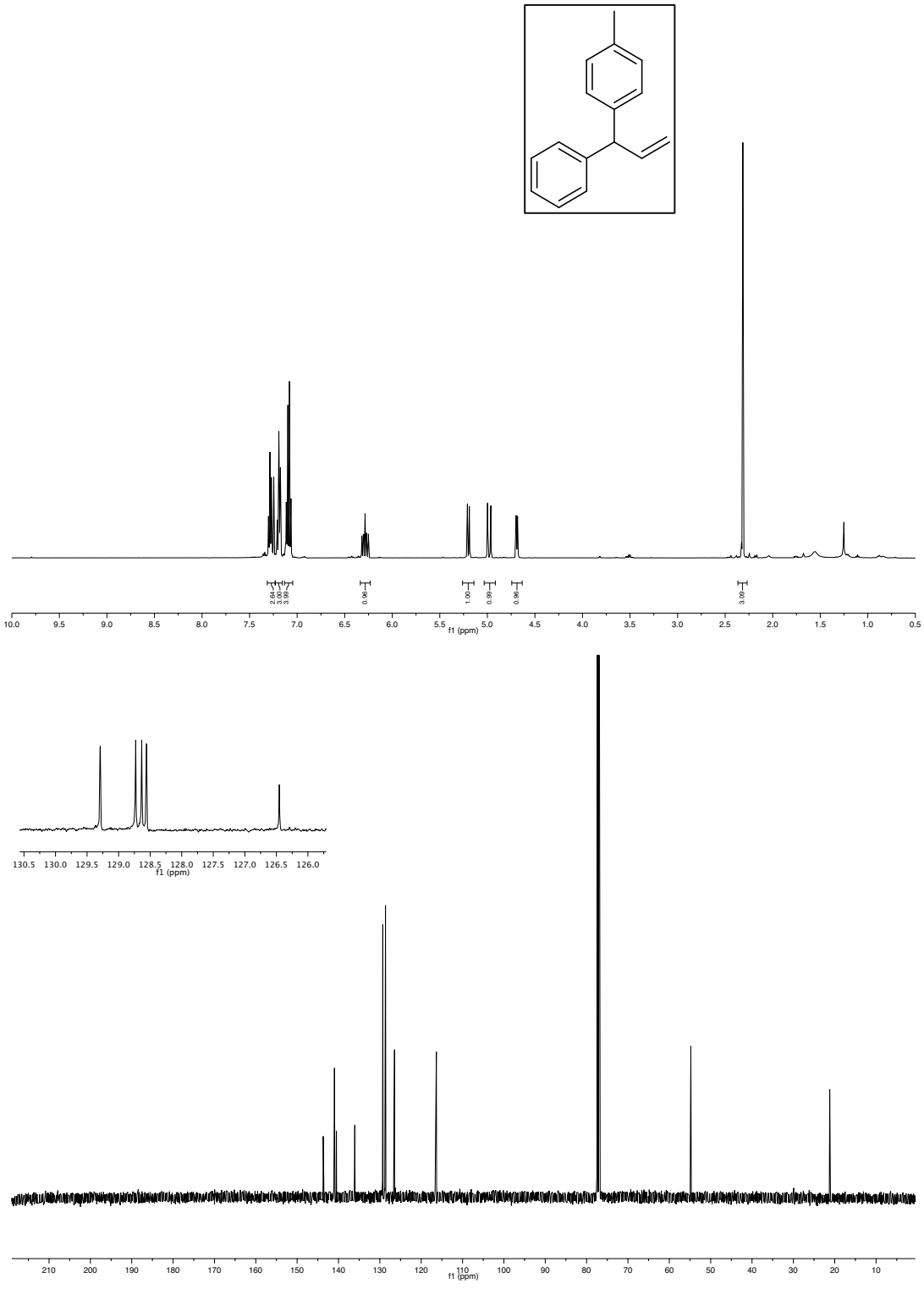


Figure S6 (**4e**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 1-methyl-4-(1-phenylallyl)benzene in $CDCl_3$.

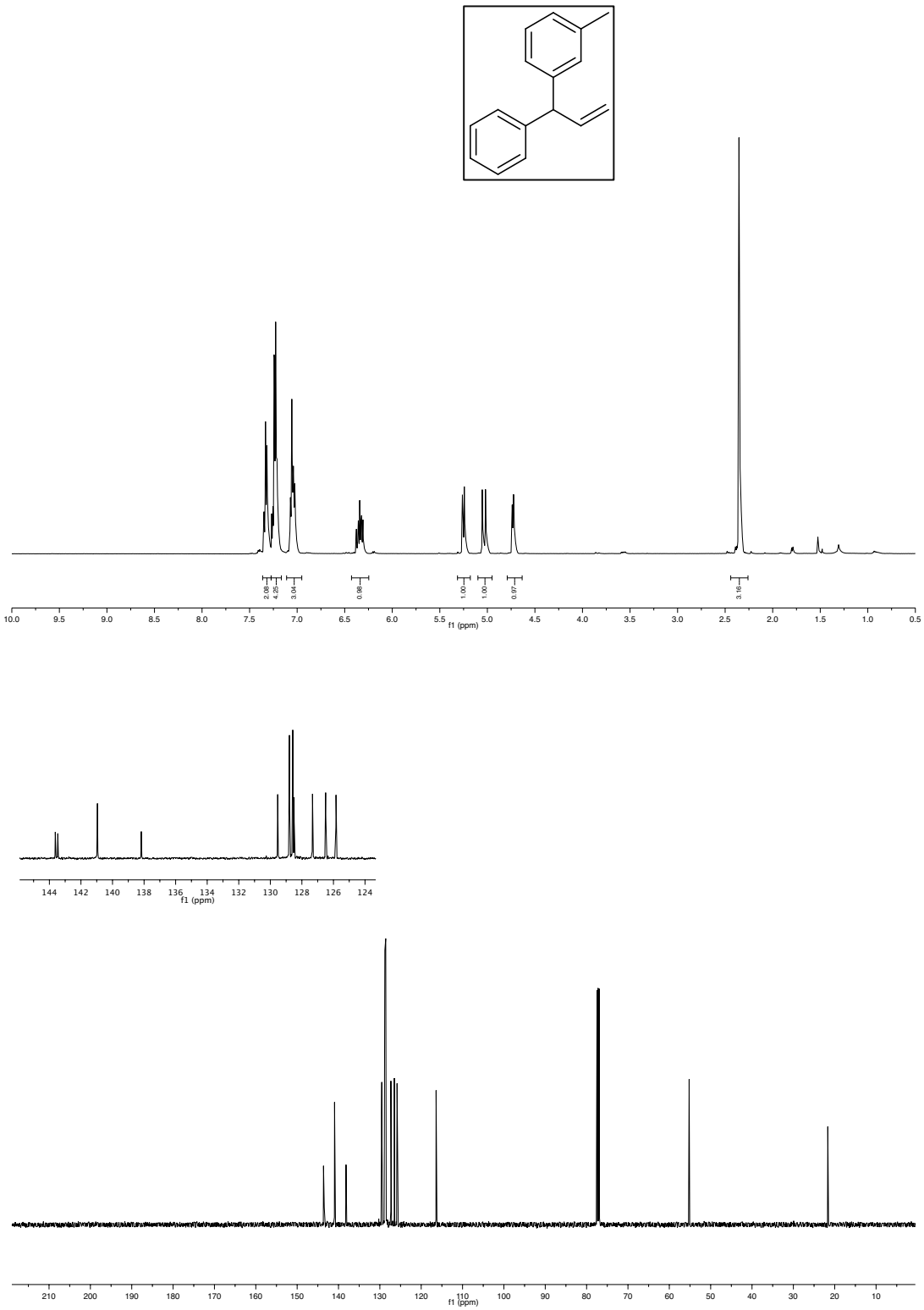


Figure S7 (**4f**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 1-methyl-3-(1-phenylallyl)benzene in $CDCl_3$.

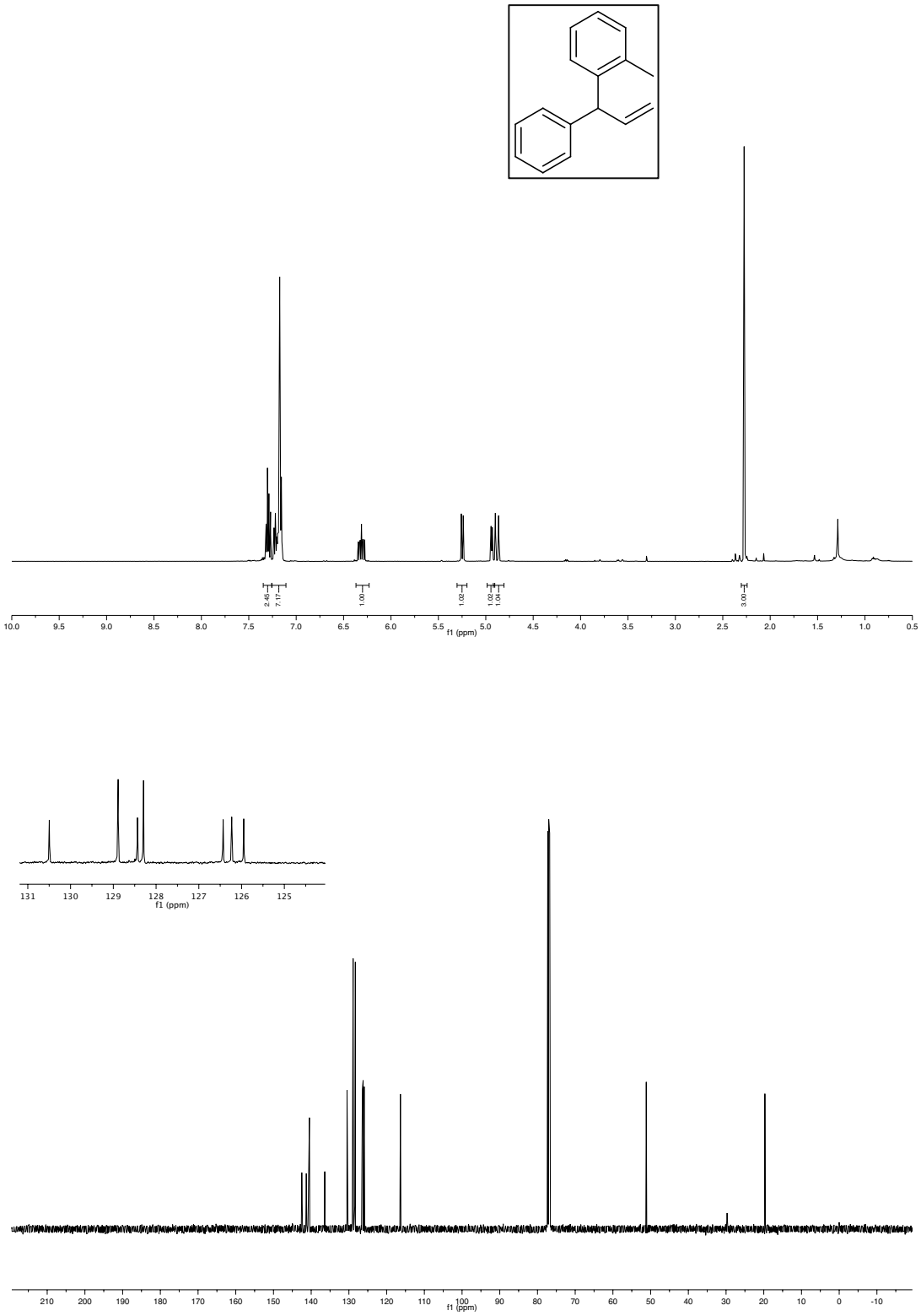


Figure S8 (**4g**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 1-methyl-2-(1-phenylallyl)benzene in $CDCl_3$.

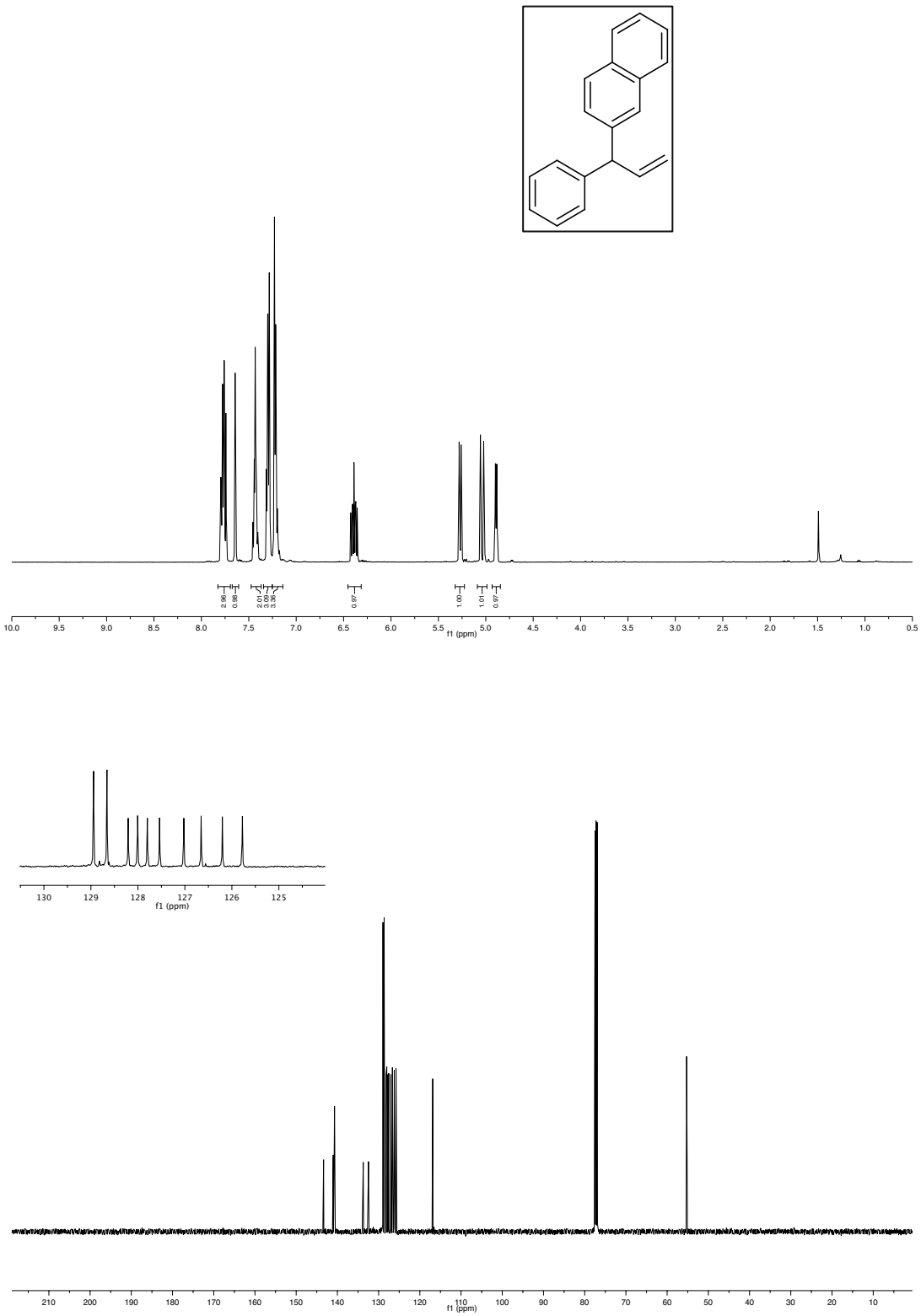


Figure S9 (**4h**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 2-(1-phenylallyl)naphthalene in $CDCl_3$.

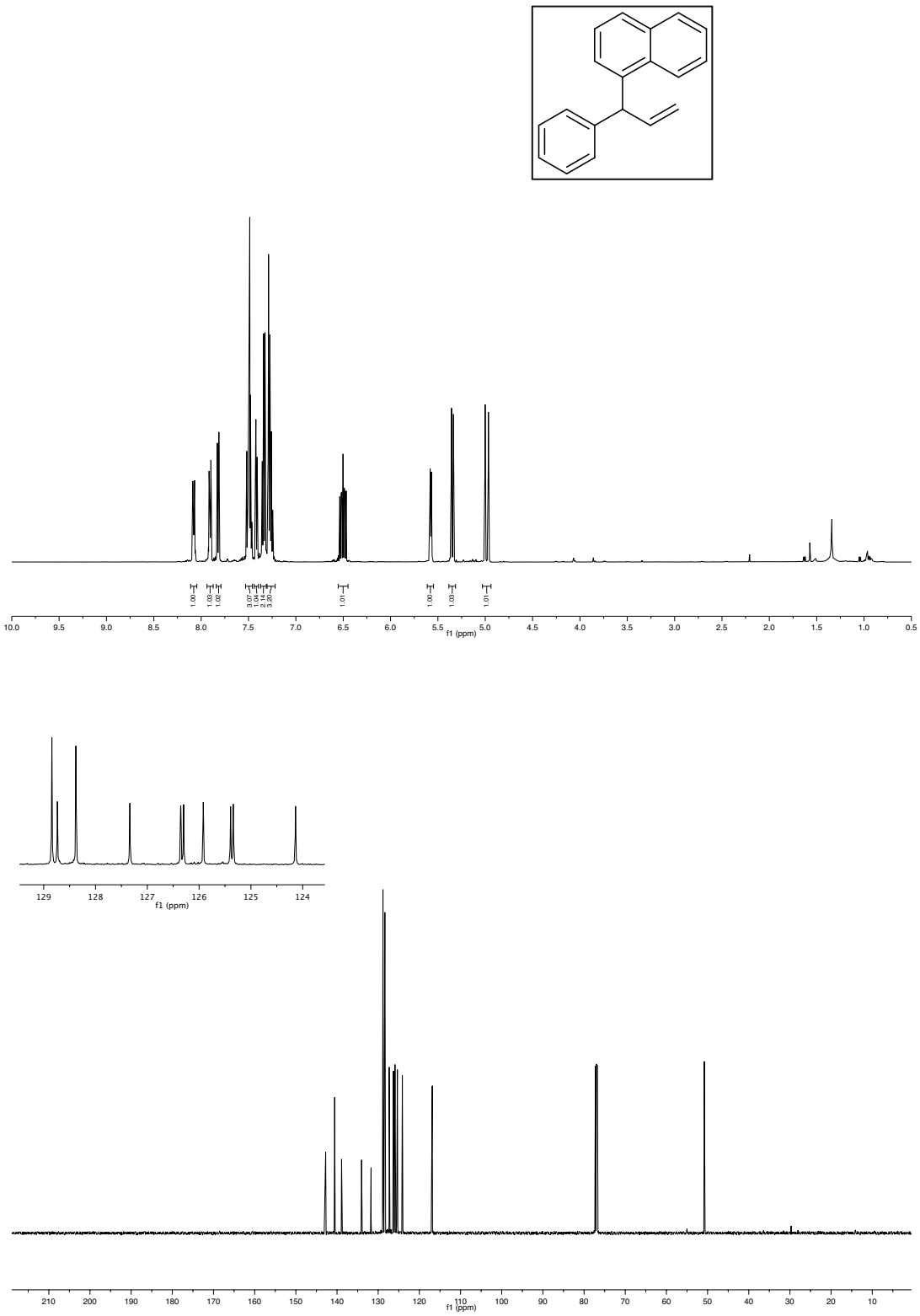


Figure S10 (**4i**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 1-(1-phenylallyl)naphthalene in $CDCl_3$.

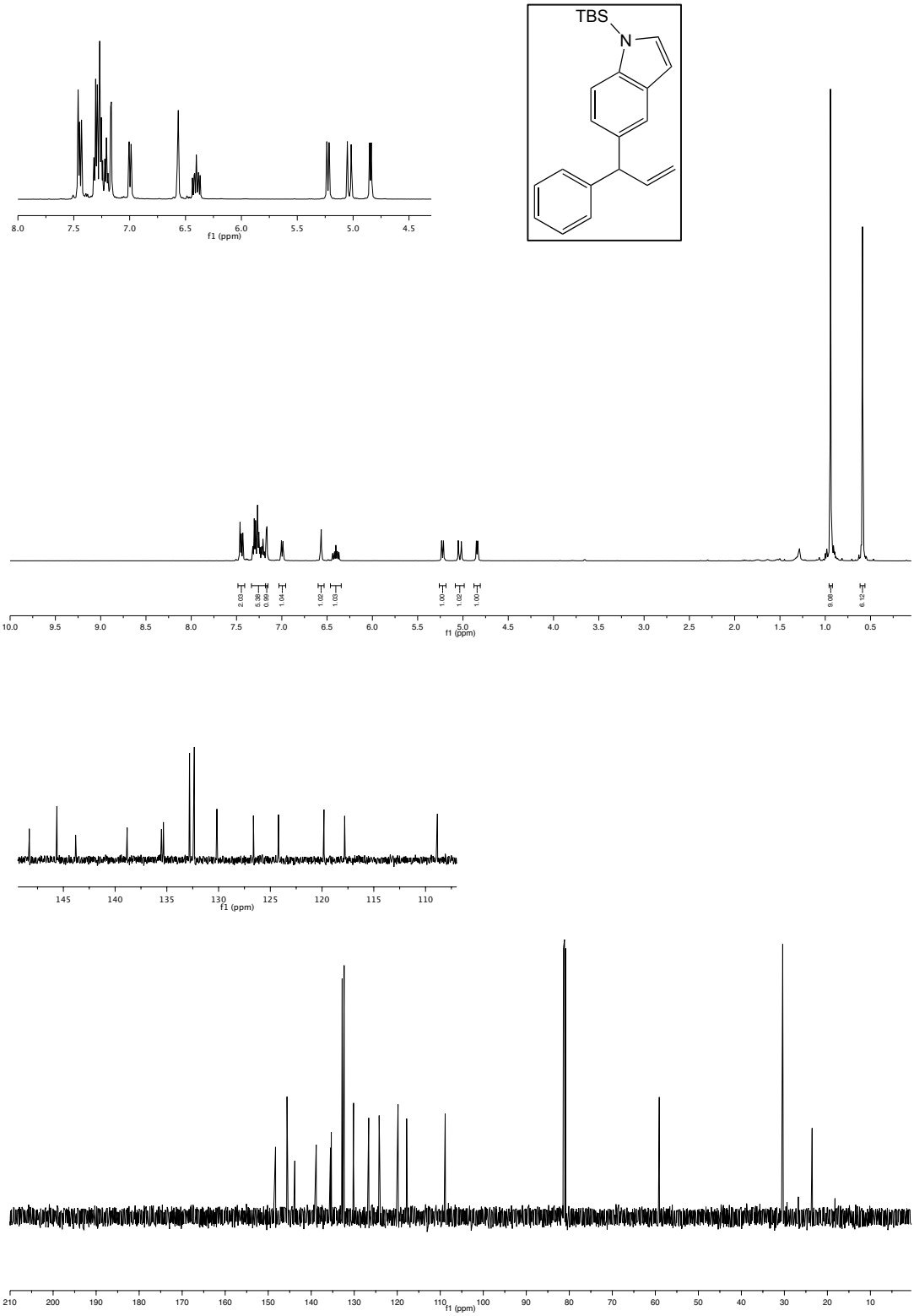


Figure S11 (**4j**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 1-(*tert*-butyldimethylsilyl)-6-(1-phenylallyl)-1H-indole in $CDCl_3$.

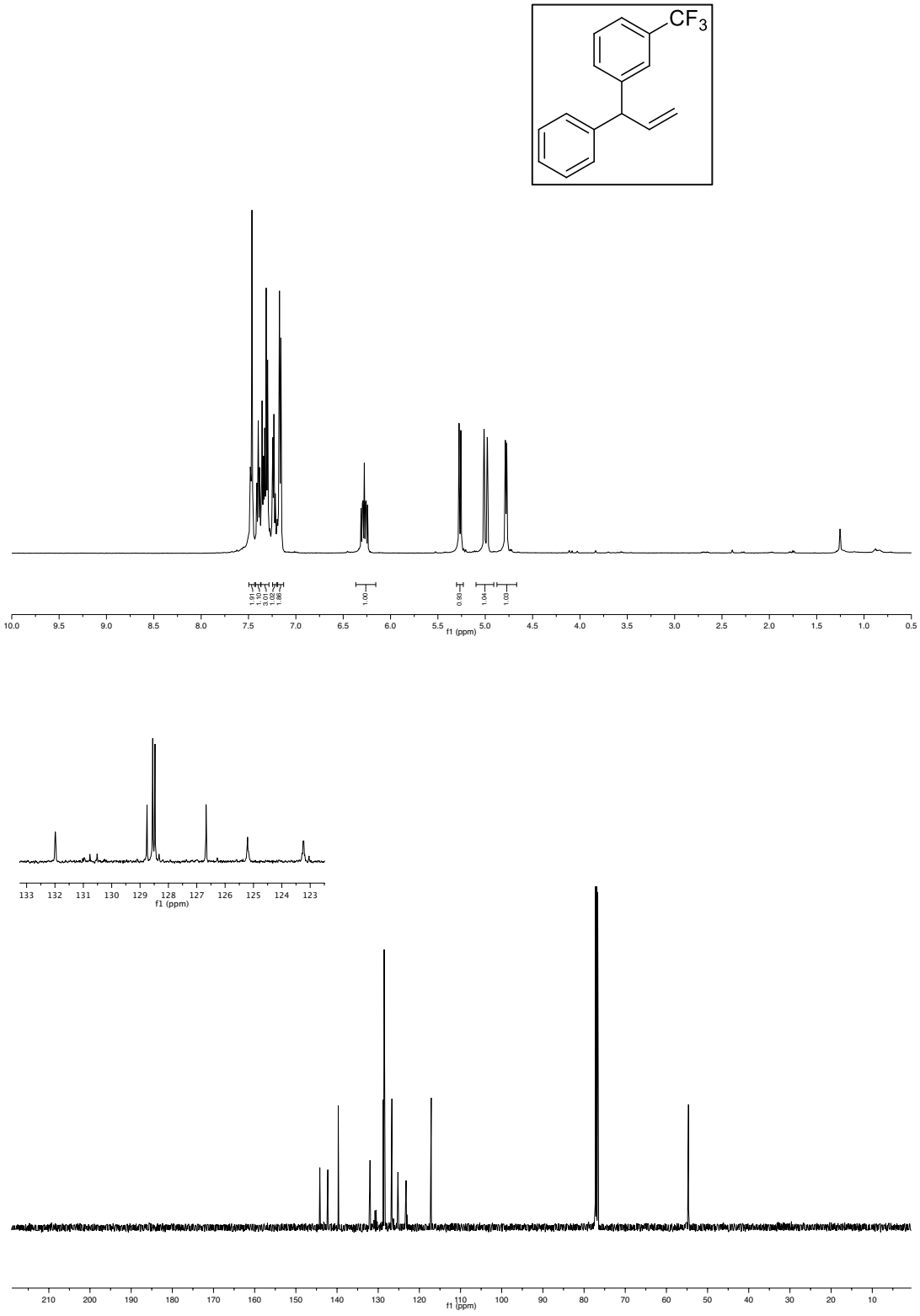


Figure S12 (**4k**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of1-(1-phenylallyl)-3-(trifluoromethyl)benzene in $CDCl_3$.

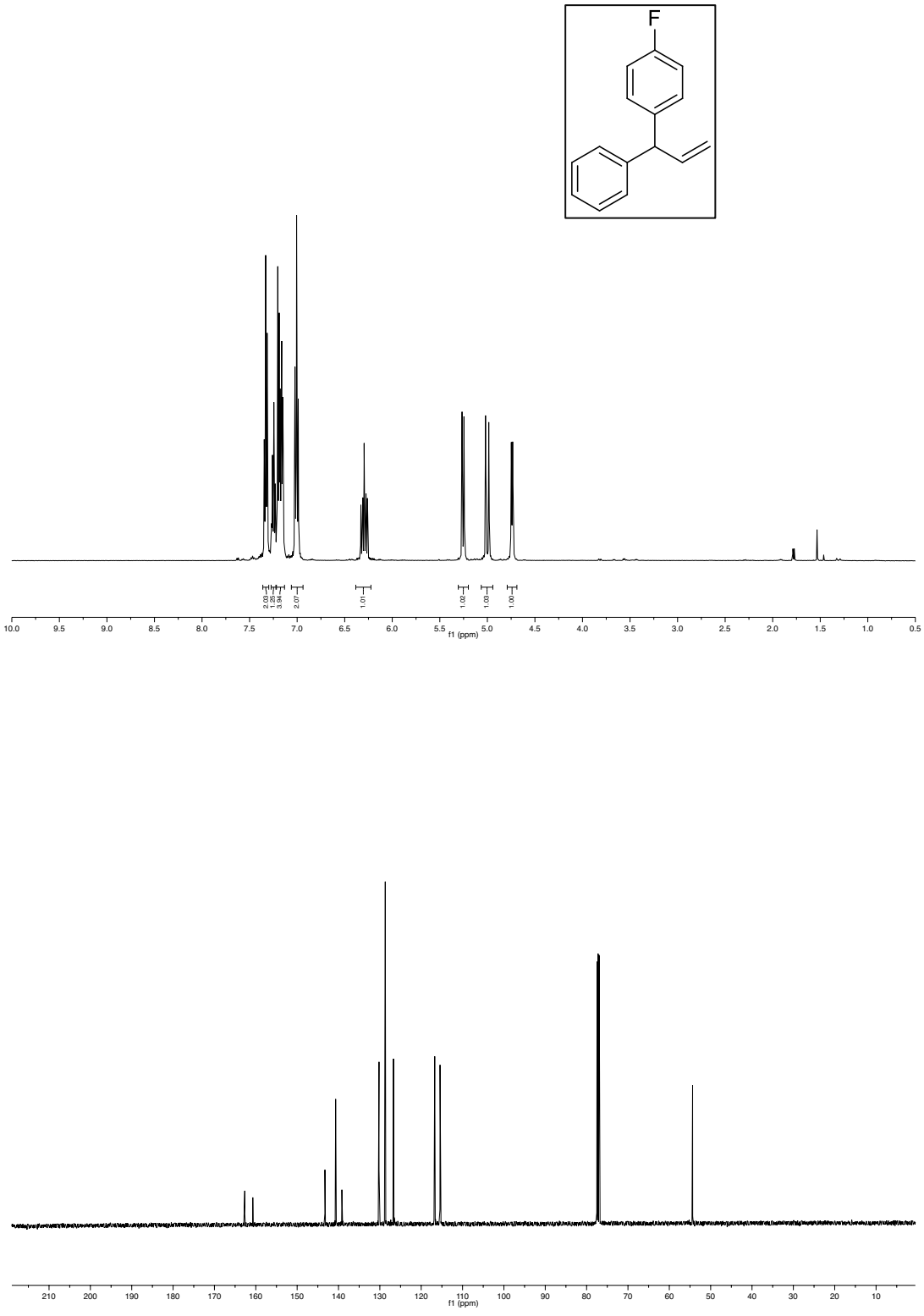


Figure S13 (**4l**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 1-fluoro-4-(1-phenylallyl)benzene in $CDCl_3$.

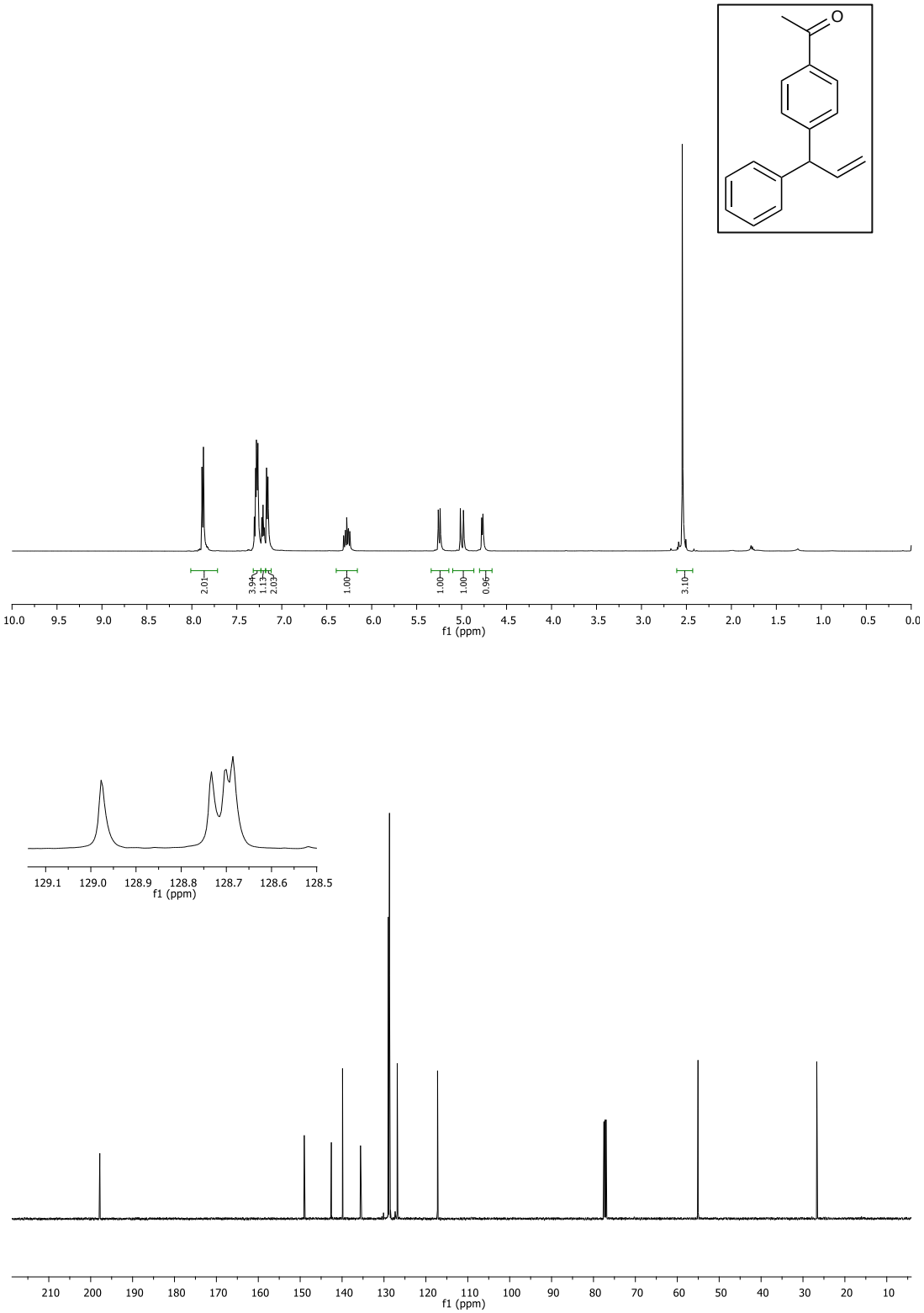


Figure S14 (**4m**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 1-(4-(1-phenylallyl)phenyl)ethan-1-one in $CDCl_3$.

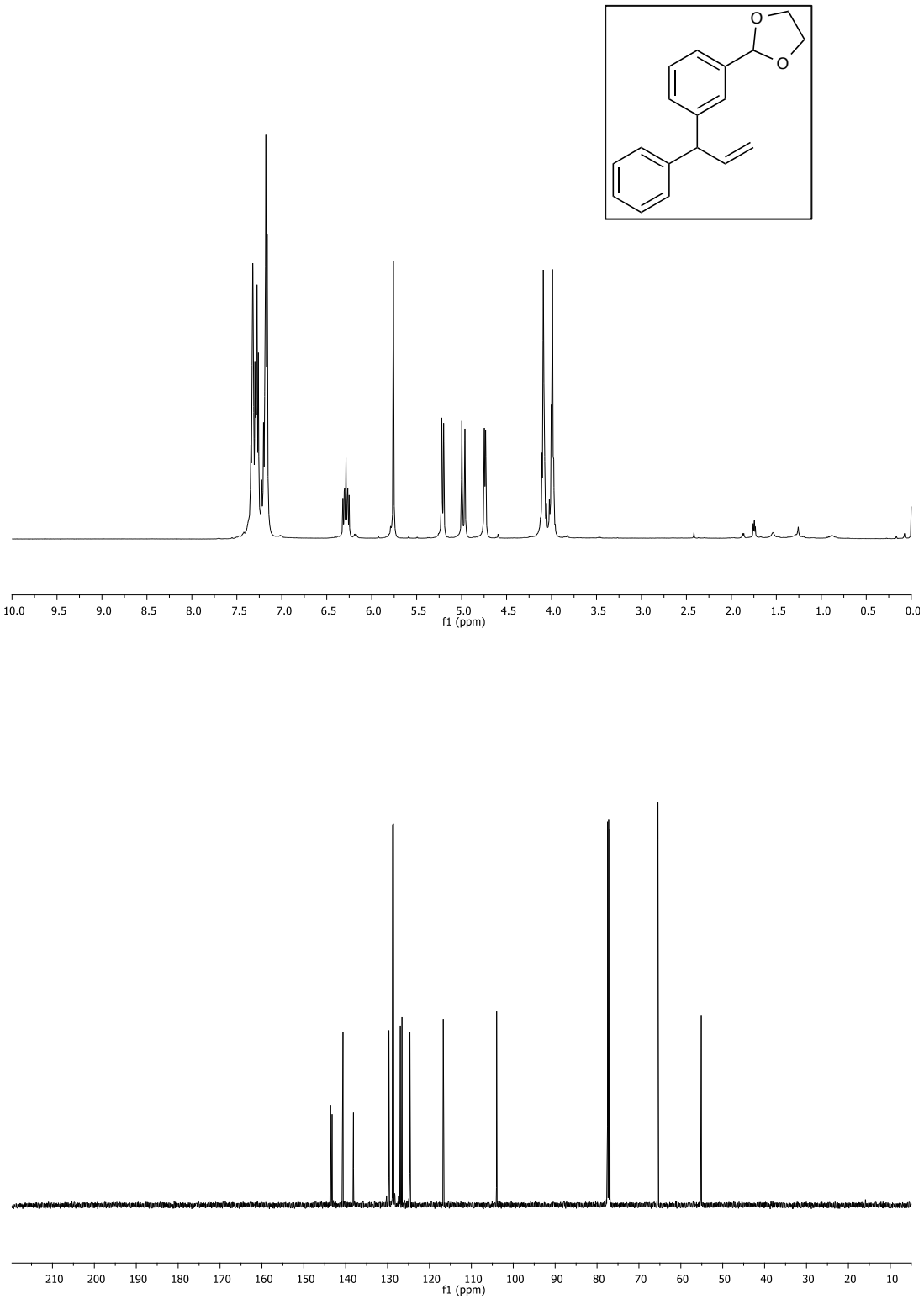


Figure S15 (**4n**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 2-(3-(1-phenylallyl)phenyl)-1,3-dioxolane in $CDCl_3$.

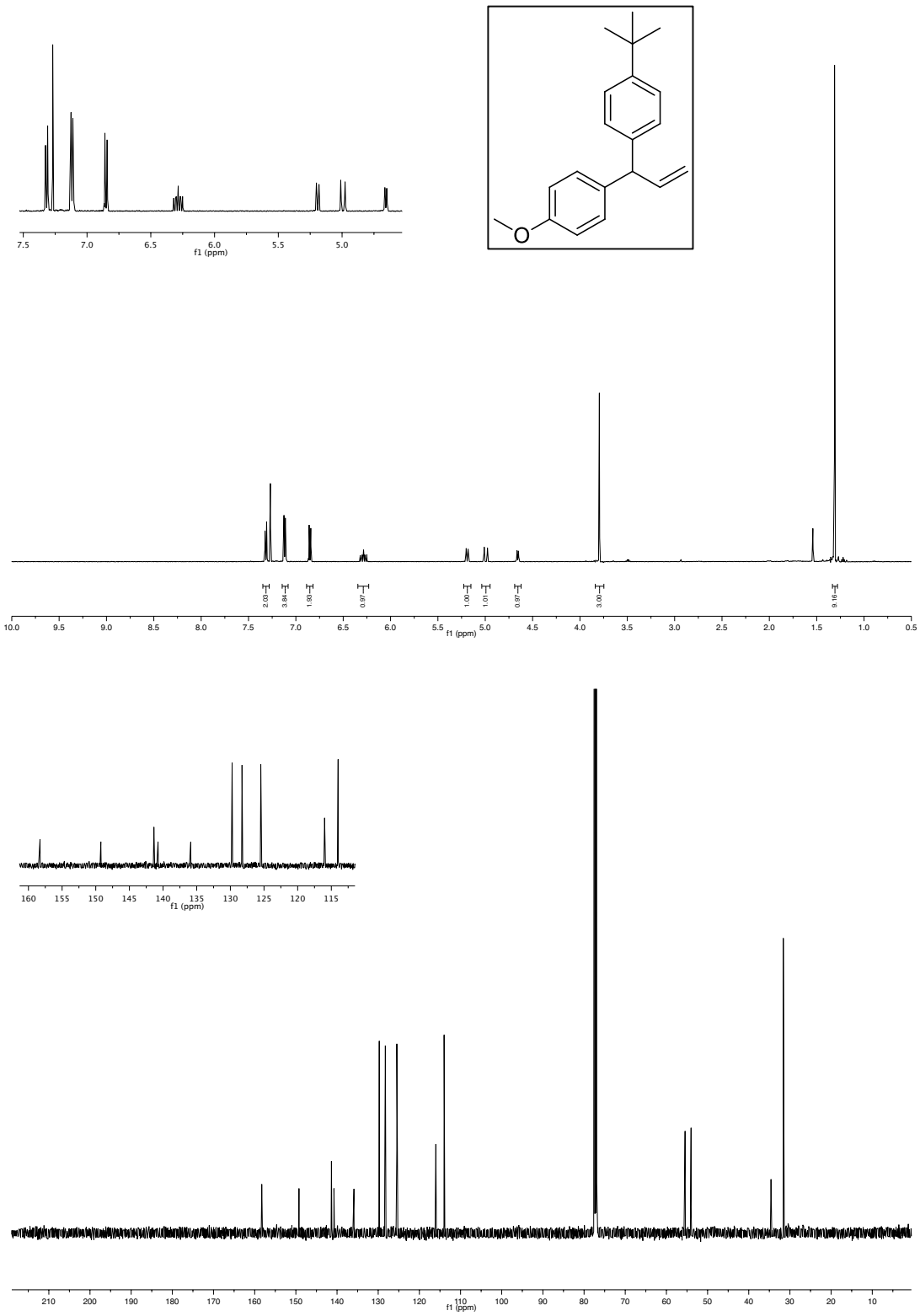


Figure S16 (**4o**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 1-(*tert*-butyl)-4-(1-(4-methoxyphenyl)allyl)benzene in $CDCl_3$.

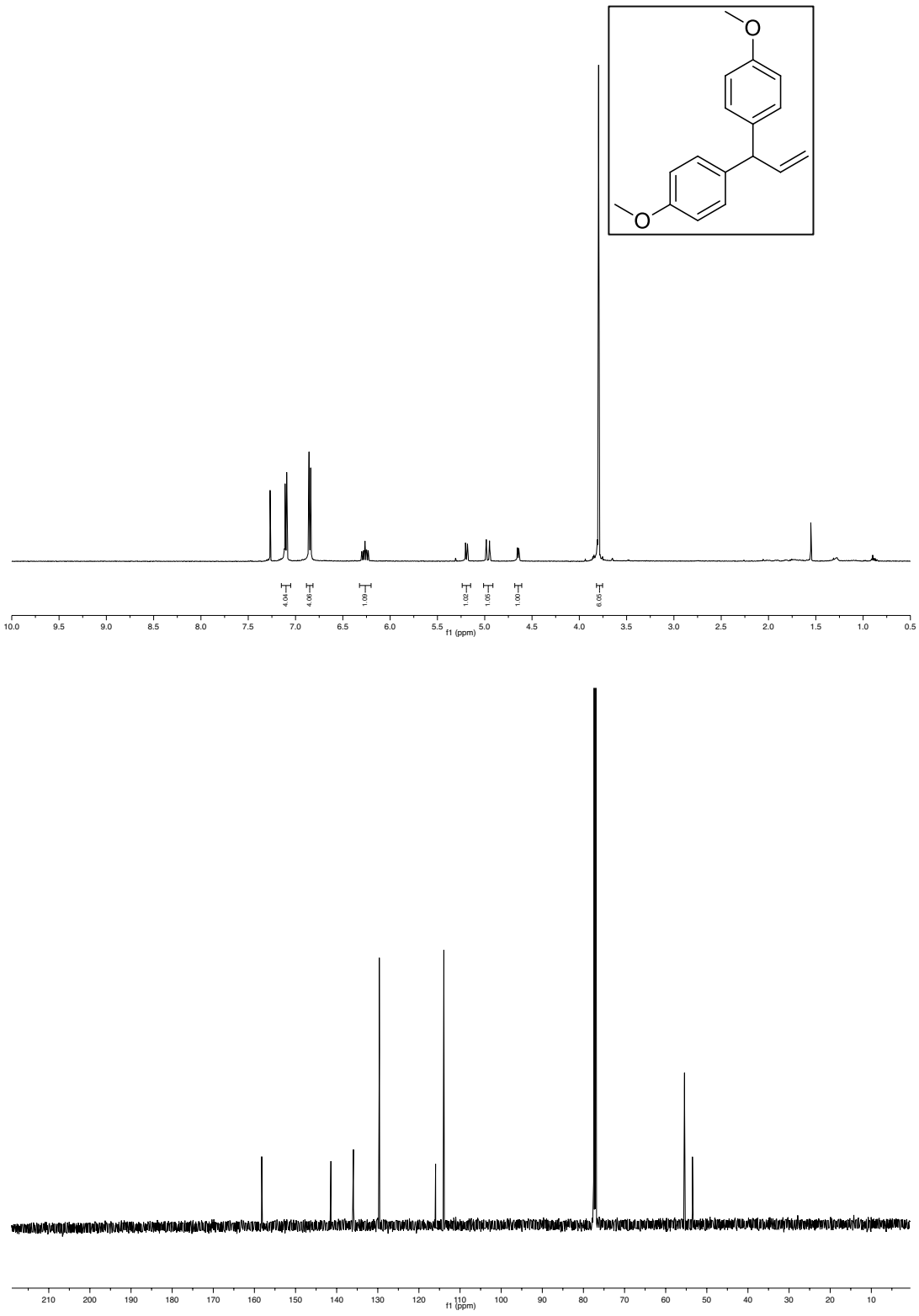


Figure S17 (**4p**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 4,4'-(prop-2-ene-1,1-diyl)bis-methoxybenzene in $CDCl_3$.

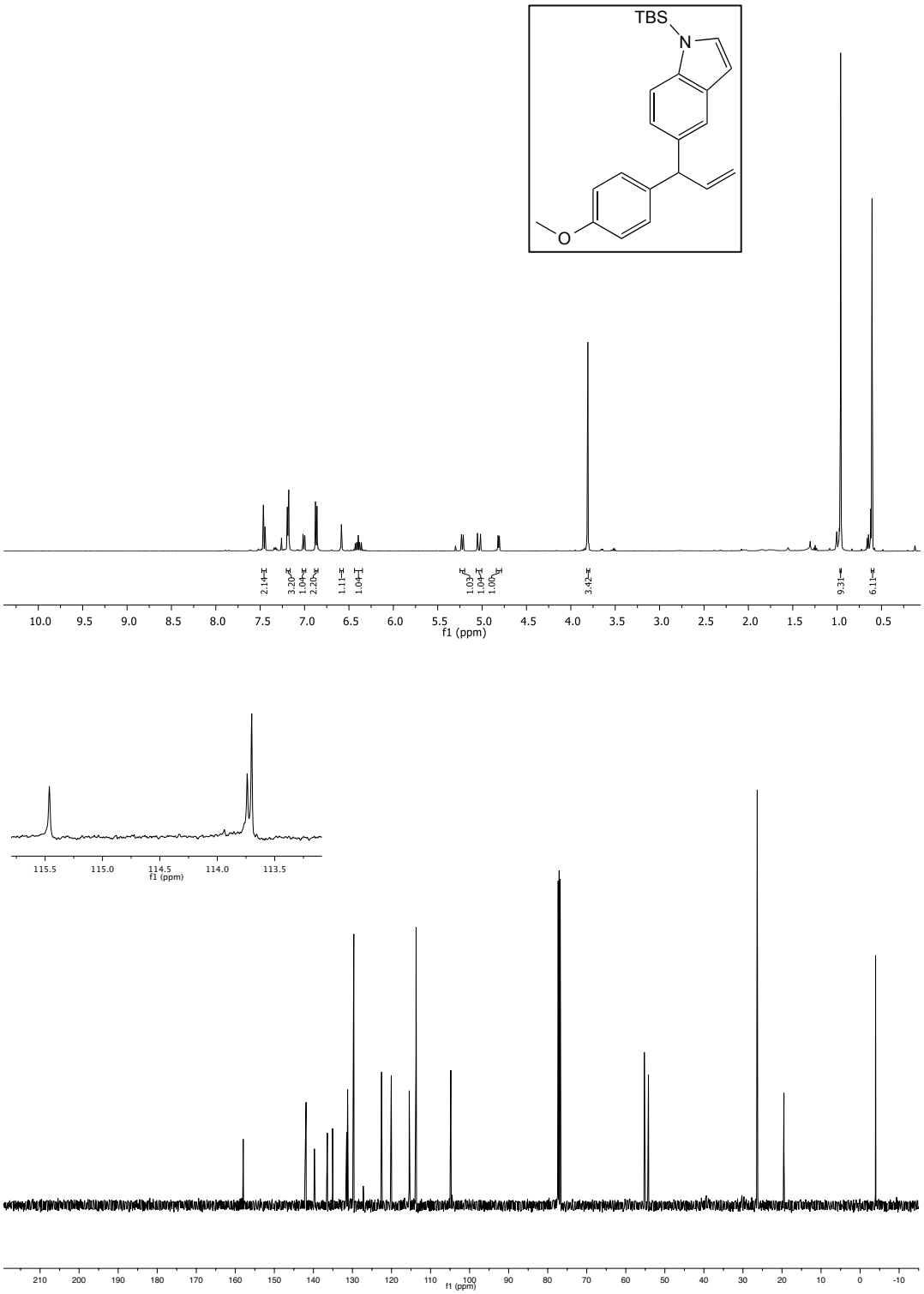


Figure S18 (**4q**) 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 1-(*tert*-butyldimethylsilyl)-5-(1-(4-methoxyphenyl)allyl)-1*H*-indole in $CDCl_3$.

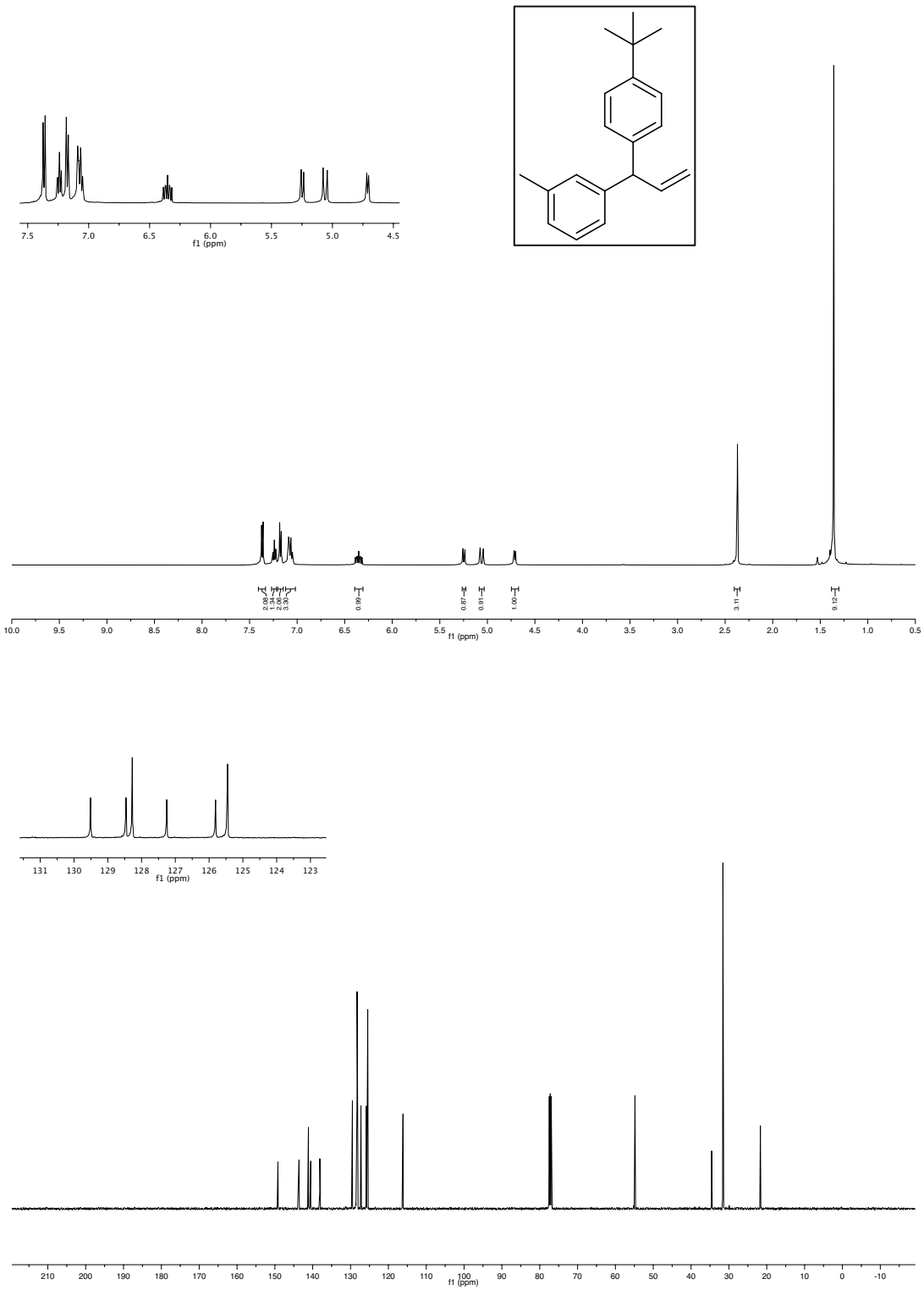


Figure S19 (**4r**) 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 1-(1-(4-(*tert*-butyl)phenyl)allyl)-3-methylbenzene in $CDCl_3$.

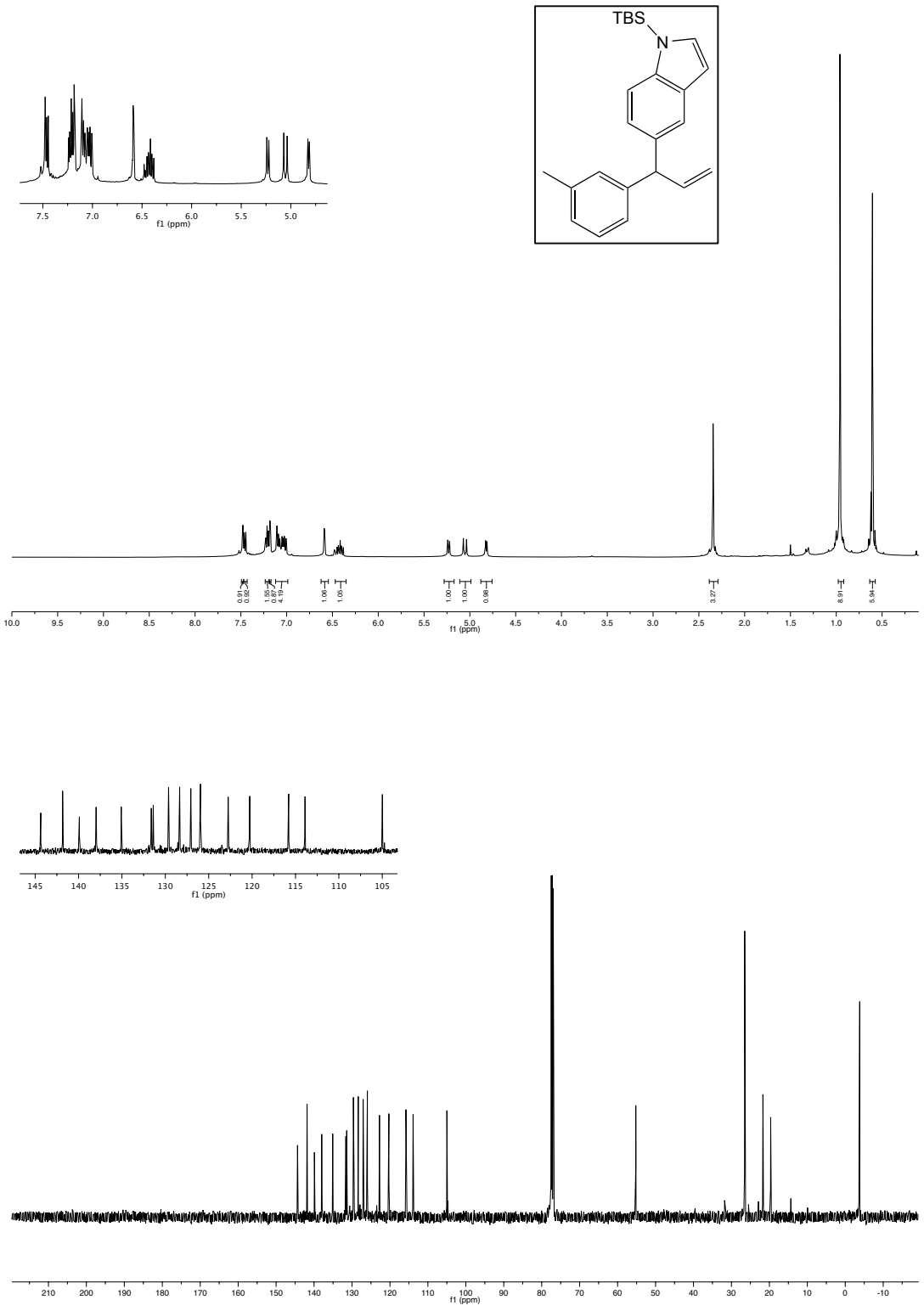


Figure S20 (**4s**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 1-(*tert*-butyldimethylsilyl)-6-(1-(m-tolyl)allyl)-1H-indole in $CDCl_3$.

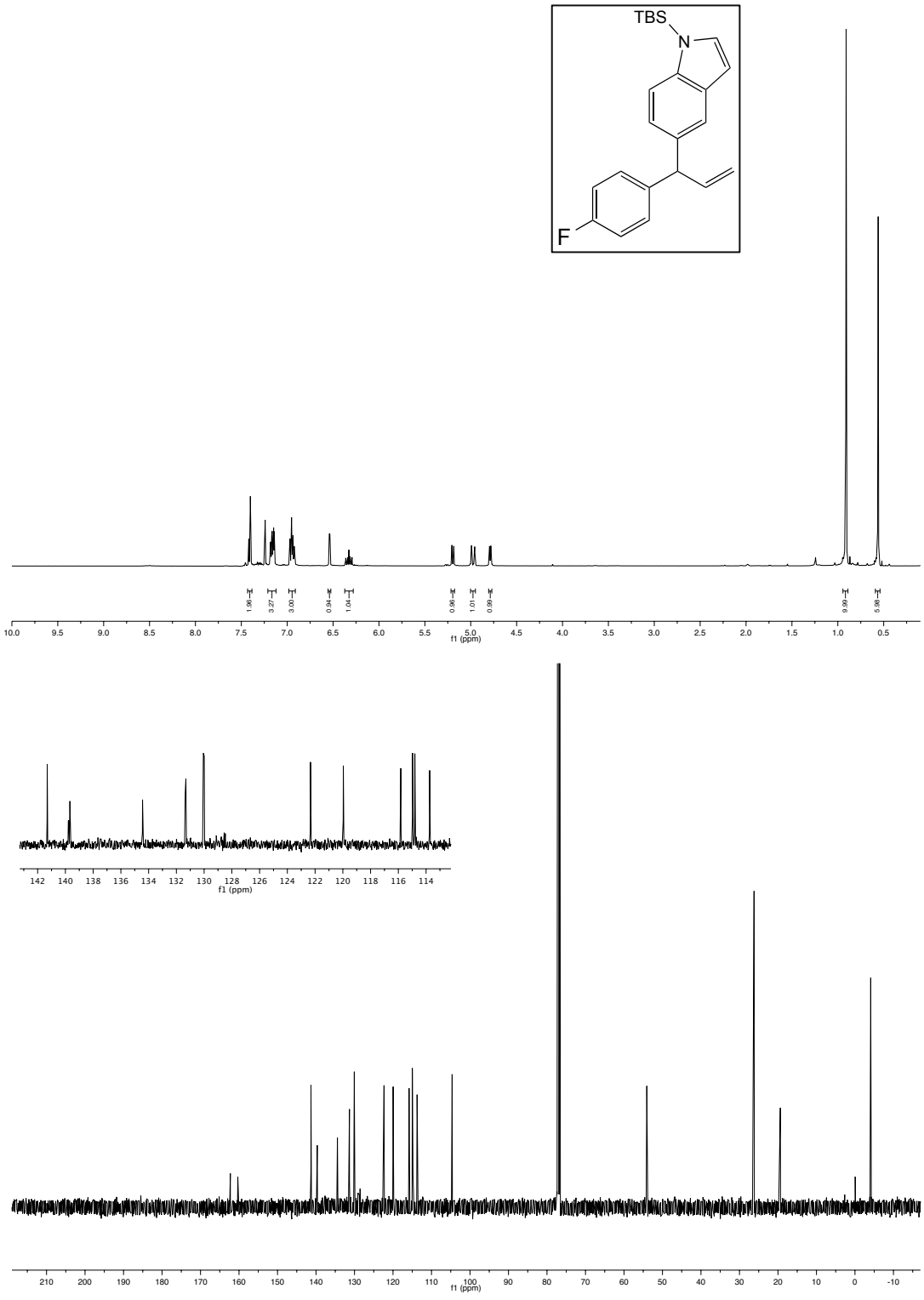


Figure S21 (**4t**). 500 MHz ^{1}H and 125 MHz ^{13}C{^{1}H} NMR of 1-(*tert*-butyldimethylsilyl)-6-(1-(4-fluorophenyl)allyl)-1H-indole in $CDCl_3$**.**

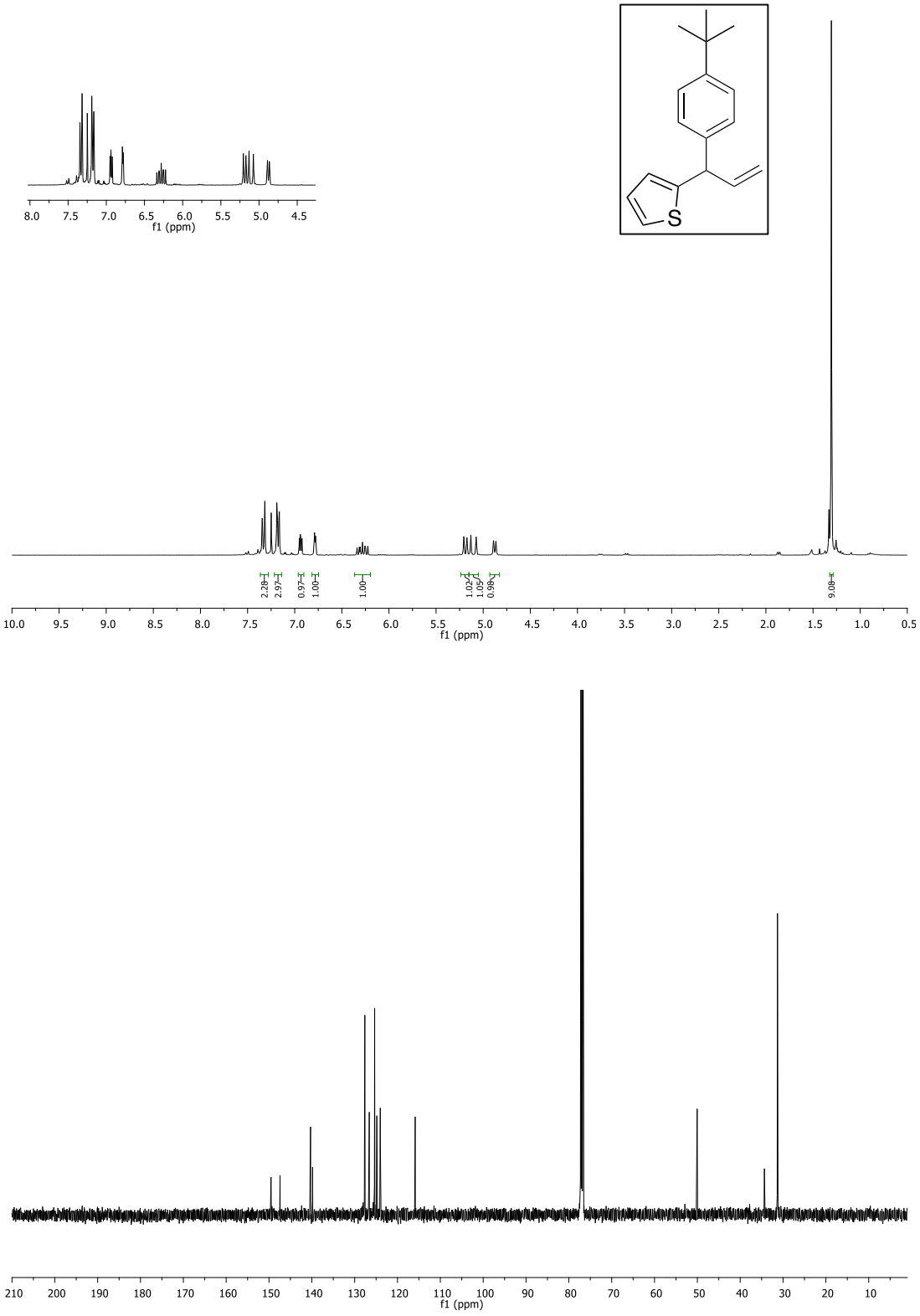


Figure S22 (**4u**). 300 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 2-(1-(4-(*tert*-butyl)phenyl)allyl)thiophene in $CDCl_3$**.**

Appendix A1 NMR Spectra Relavant to Chapter 2

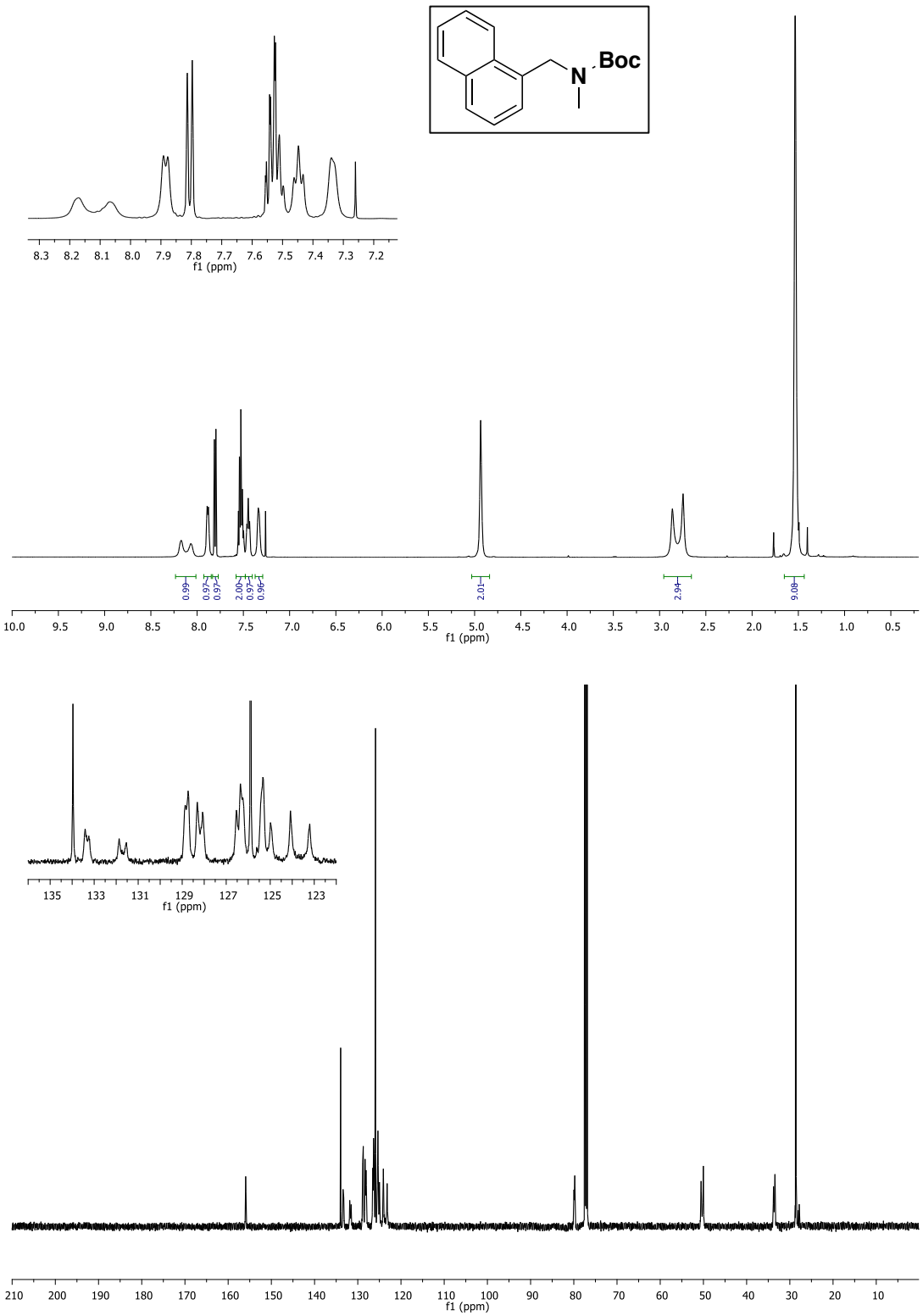


Figure S1 (**1g**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-Butyl methyl(naphthalen-1-ylmethyl)carbamate in $CDCl_3$.

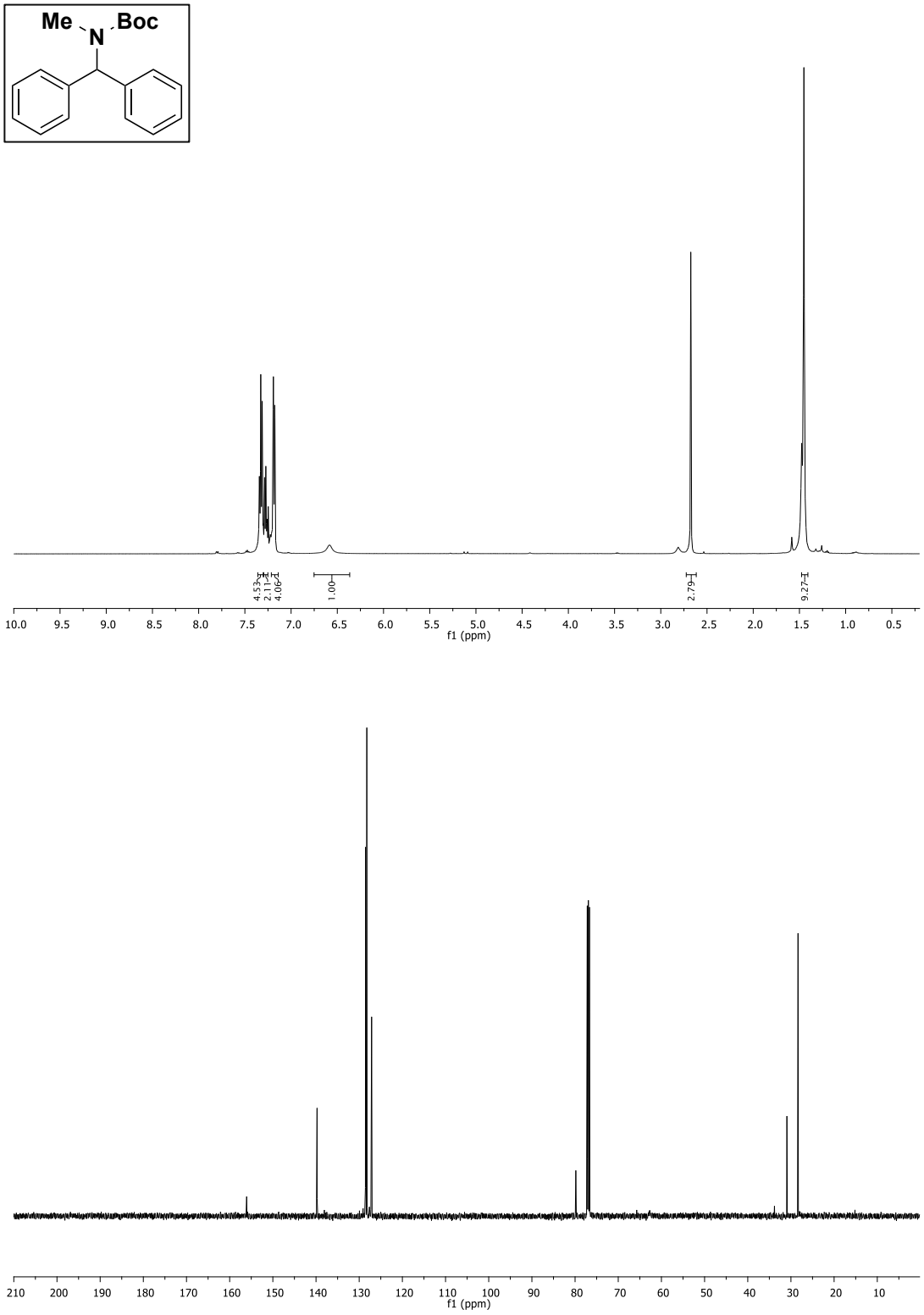


Figure S1 (**4a**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl benzhydryl(methyl)carbamate in $CDCl_3$.

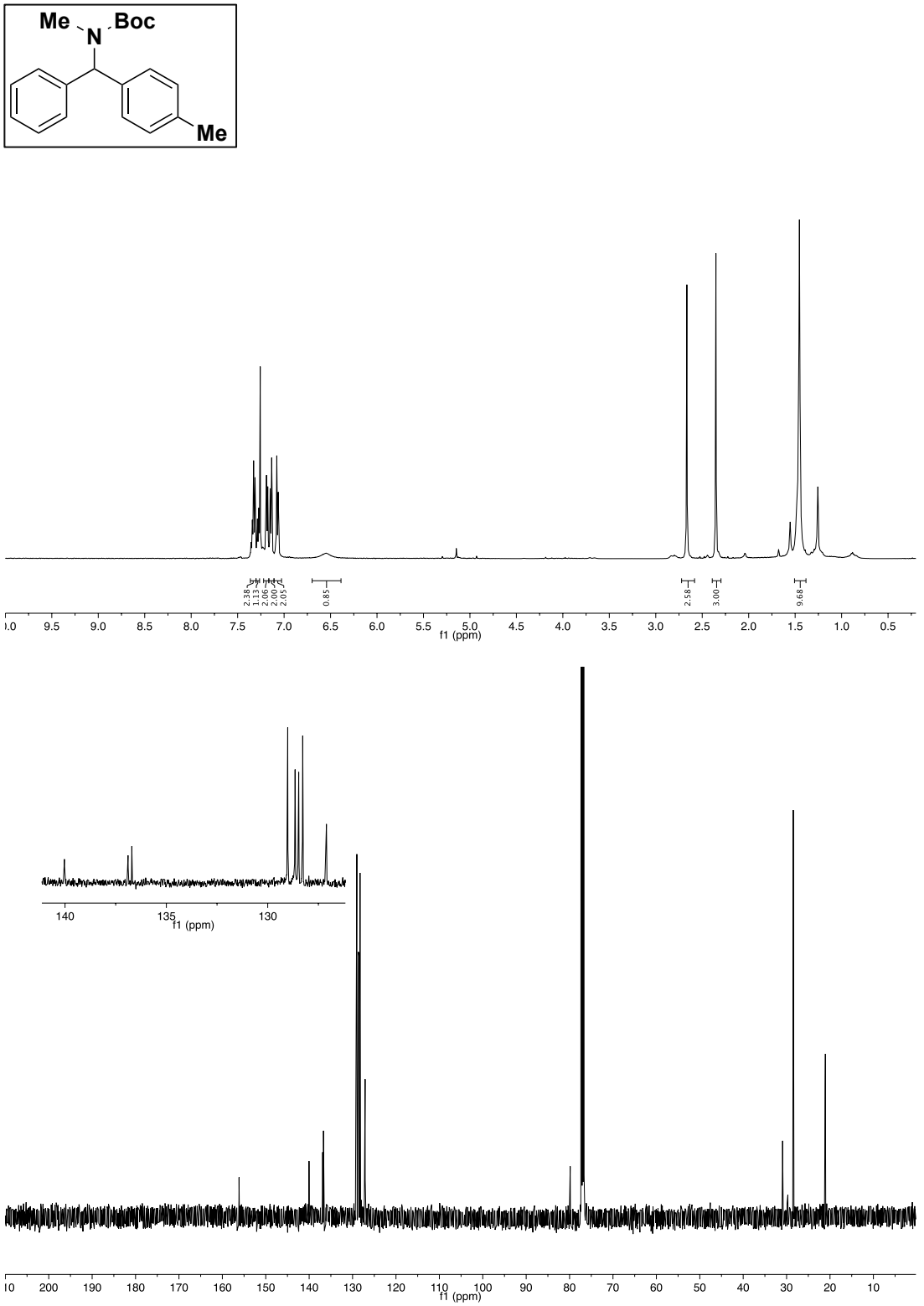


Figure S2 (**4b**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl methyl(phenyl(*p*-tolyl)methyl)carbamate in $CDCl_3$.

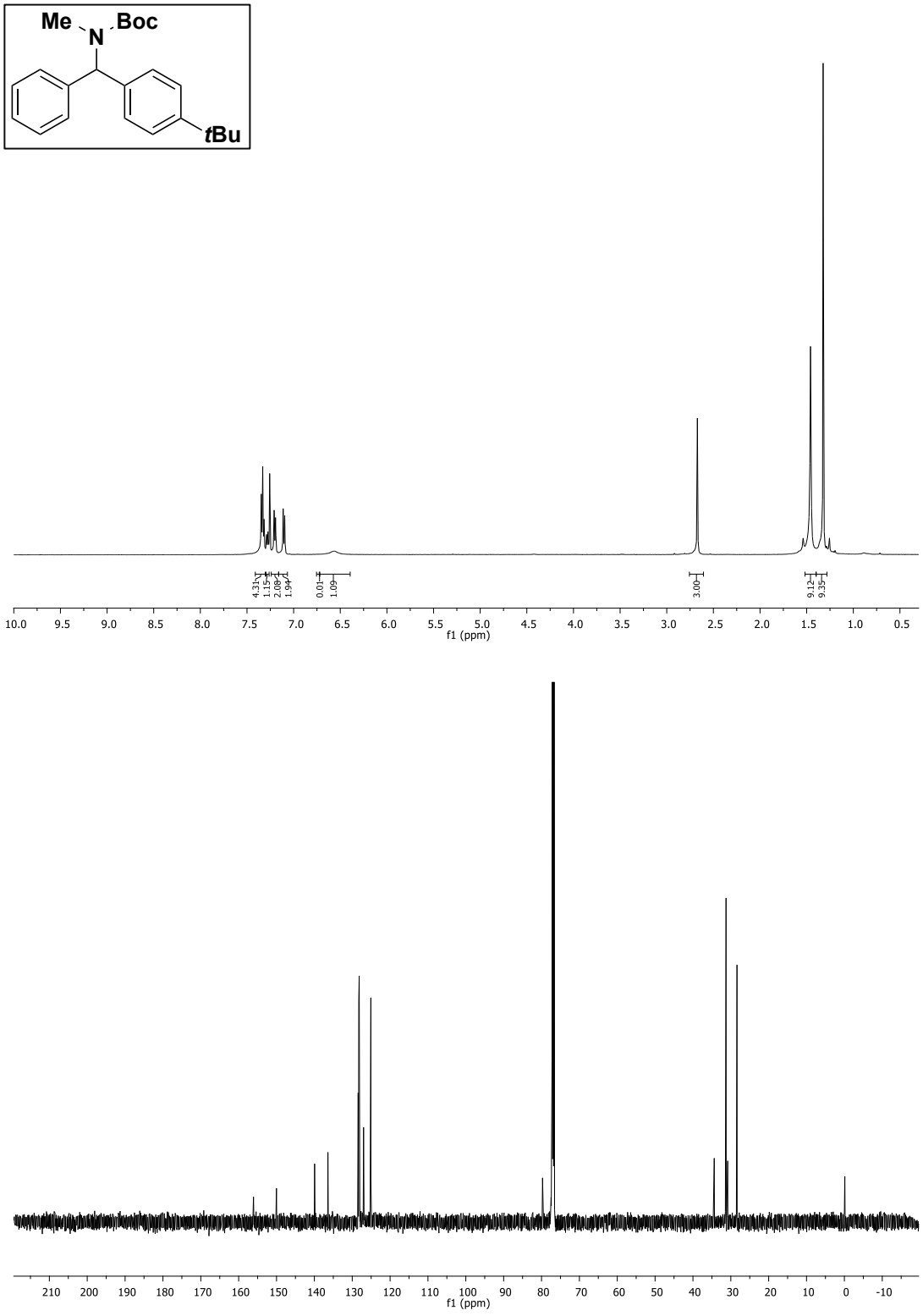


Figure S3 (**4c**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl ((4-(*tert*-butyl)phenyl)(phenyl)methyl)(methyl)carbamate in $CDCl_3$.

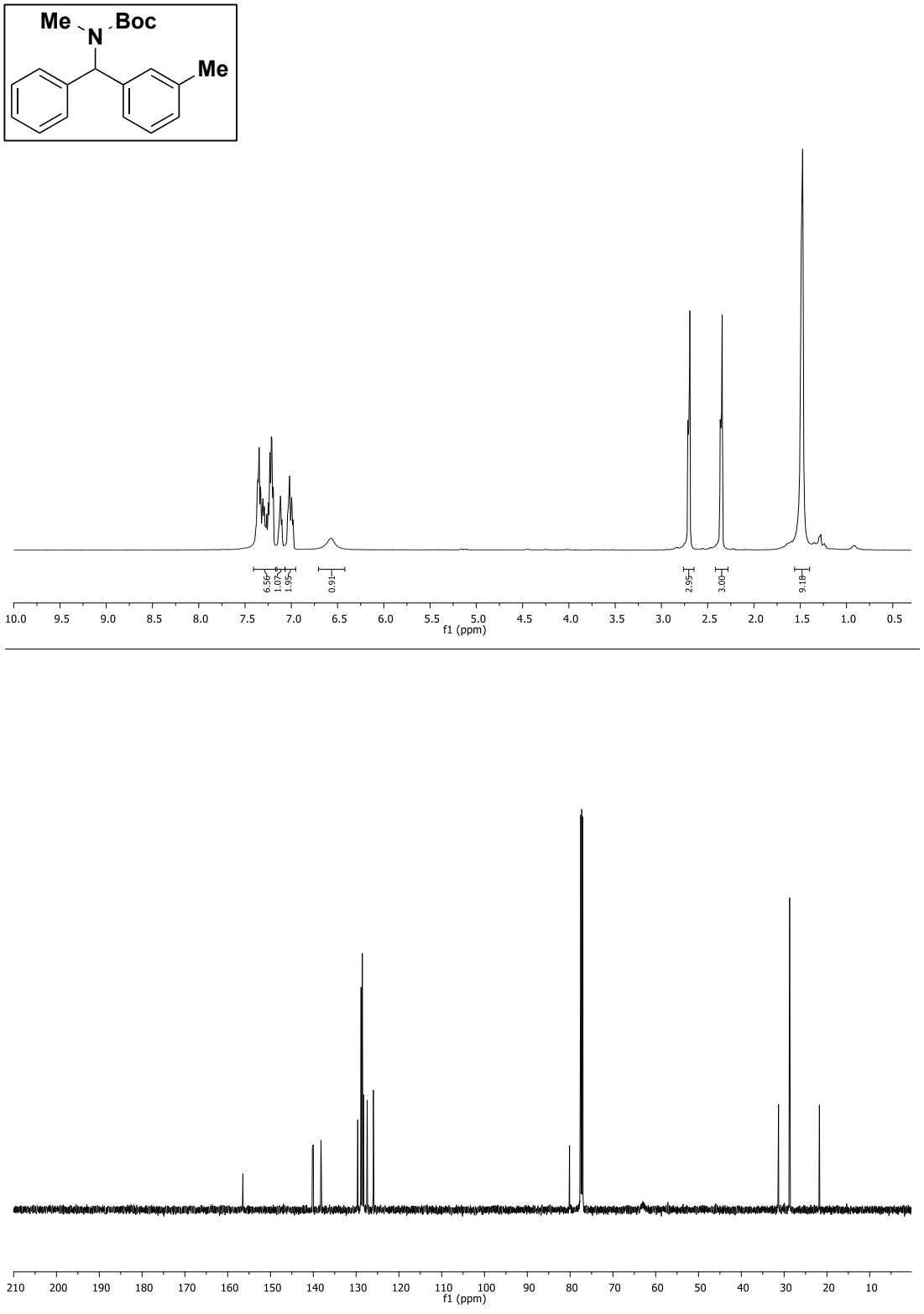
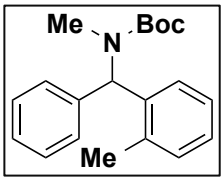


Figure S4 (**4d**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl methyl(phenyl(*m*-tolyl)methyl)carbamate in $CDCl_3$.



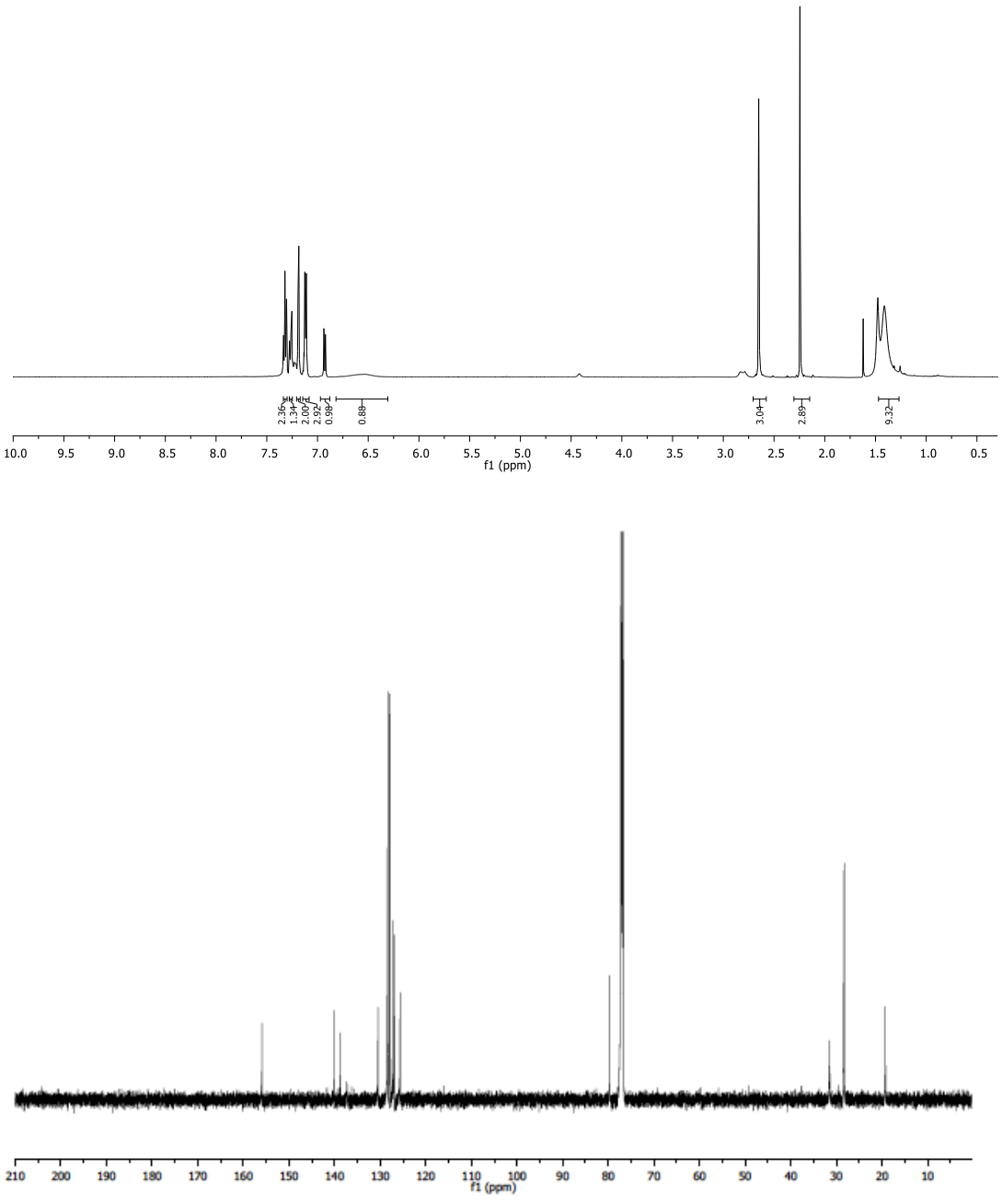


Figure S5 (**4e**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl methyl(phenyl(*o*-tolyl)methyl)carbamate in $CDCl_3$.

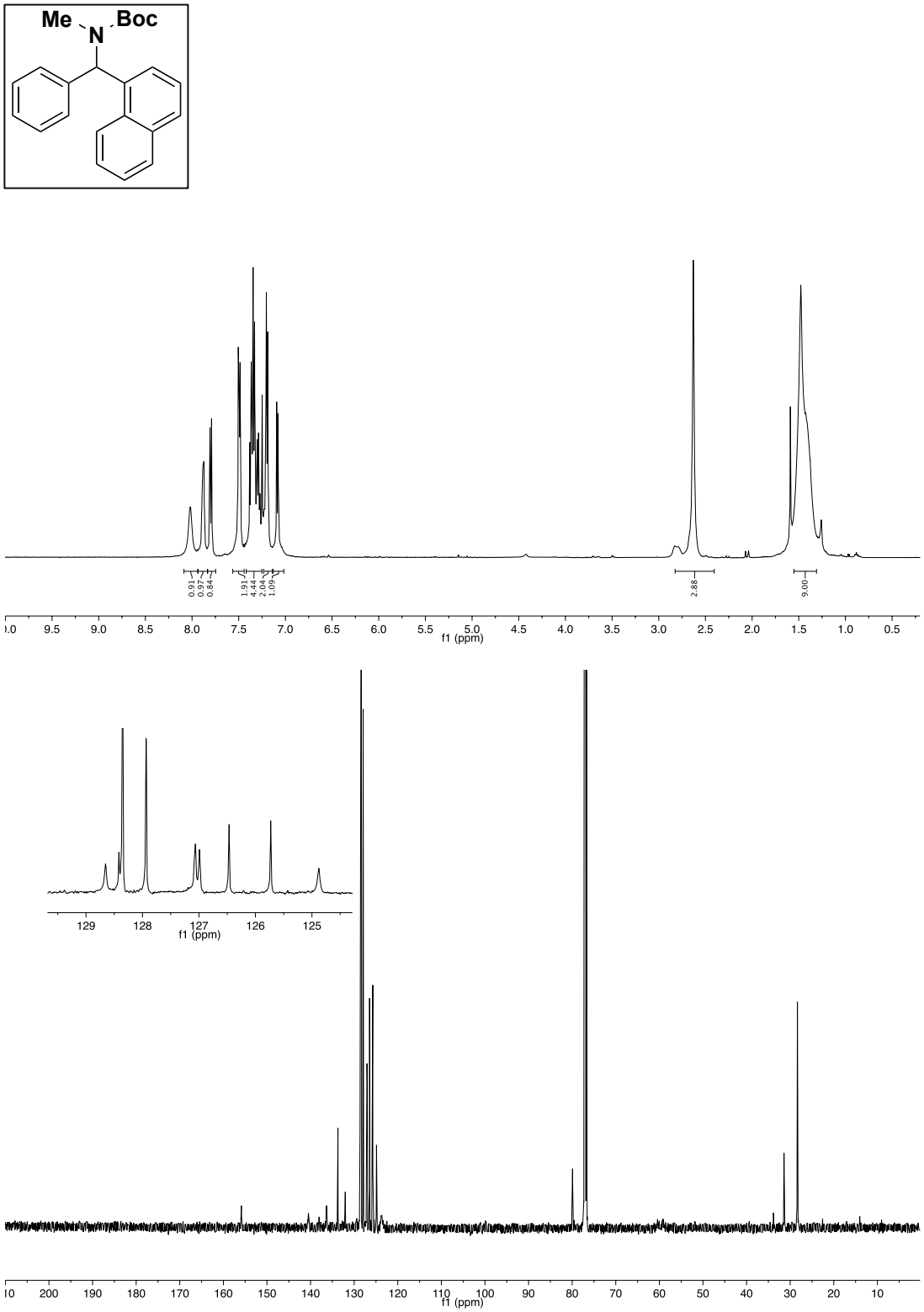


Figure S6 (**4f**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl methyl(naphthalen-1-yl(phenyl)methyl)carbamate in $CDCl_3$.

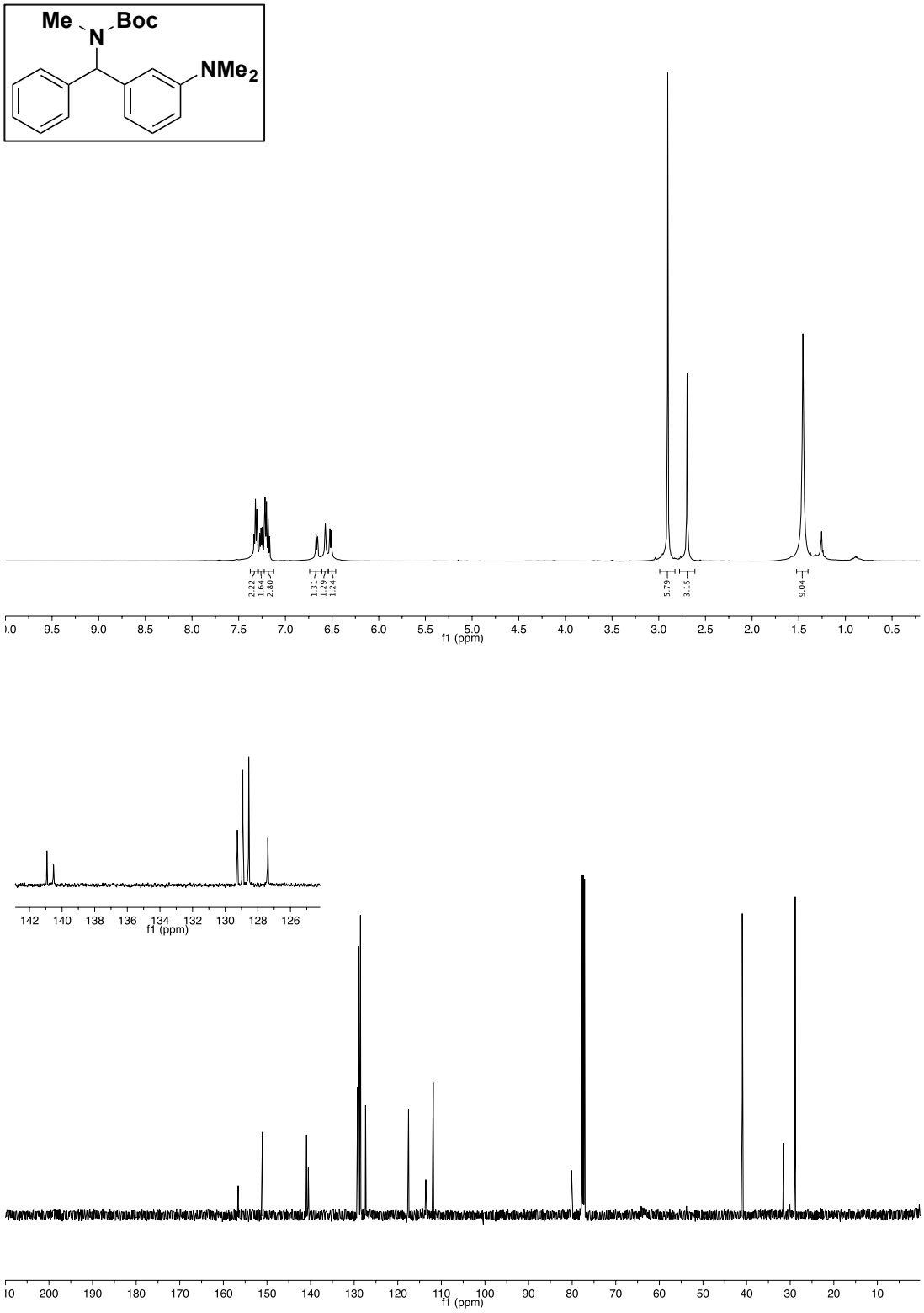
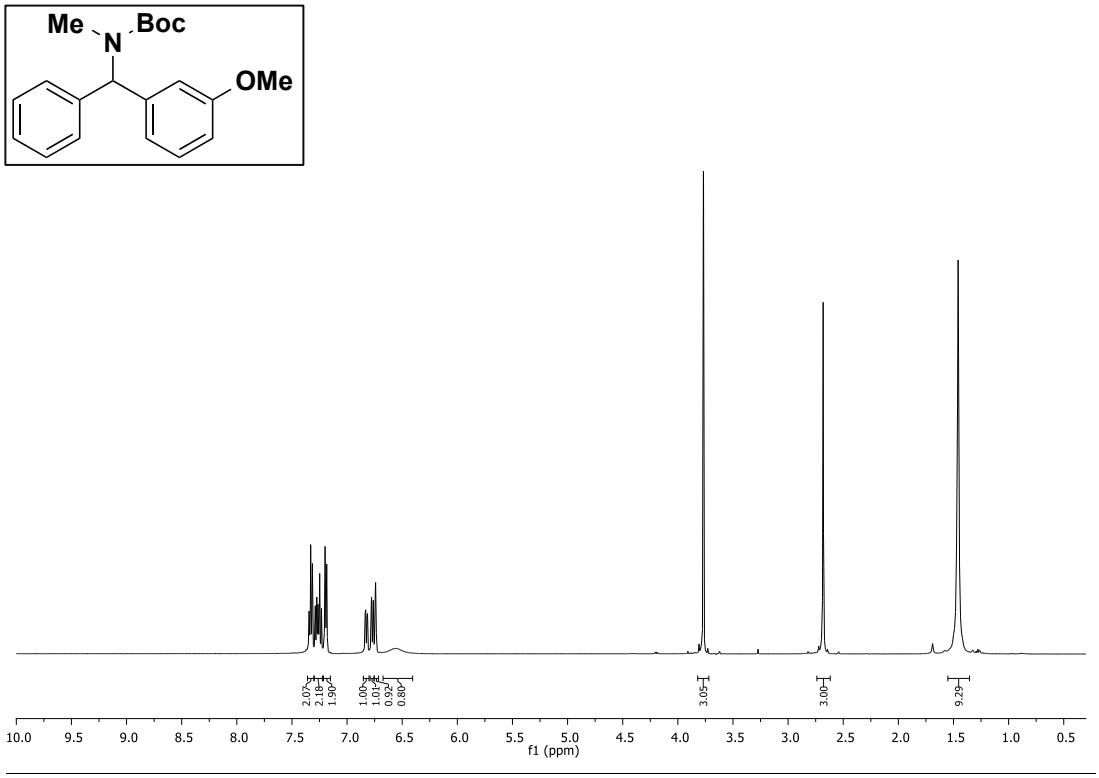


Figure S7 (**4g**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl ((3-(dimethylamino)phenyl)(phenyl)methyl)(methyl)carbamate in $CDCl_3$.



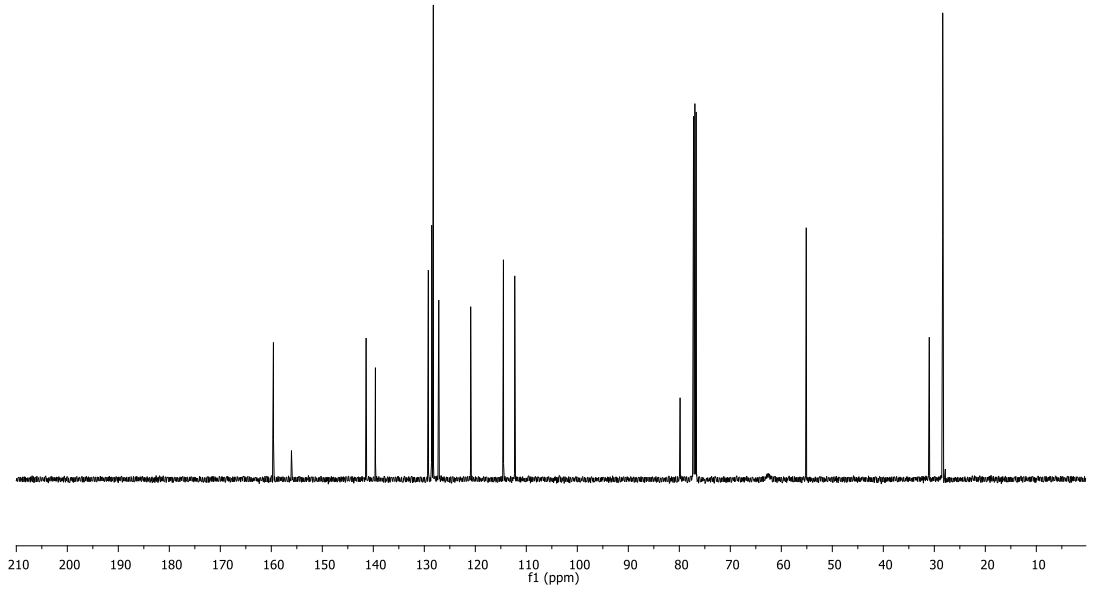


Figure S8 (**4h**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl ((3-methoxyphenyl)(phenyl)methyl)(methyl)carbamate in $CDCl_3$.

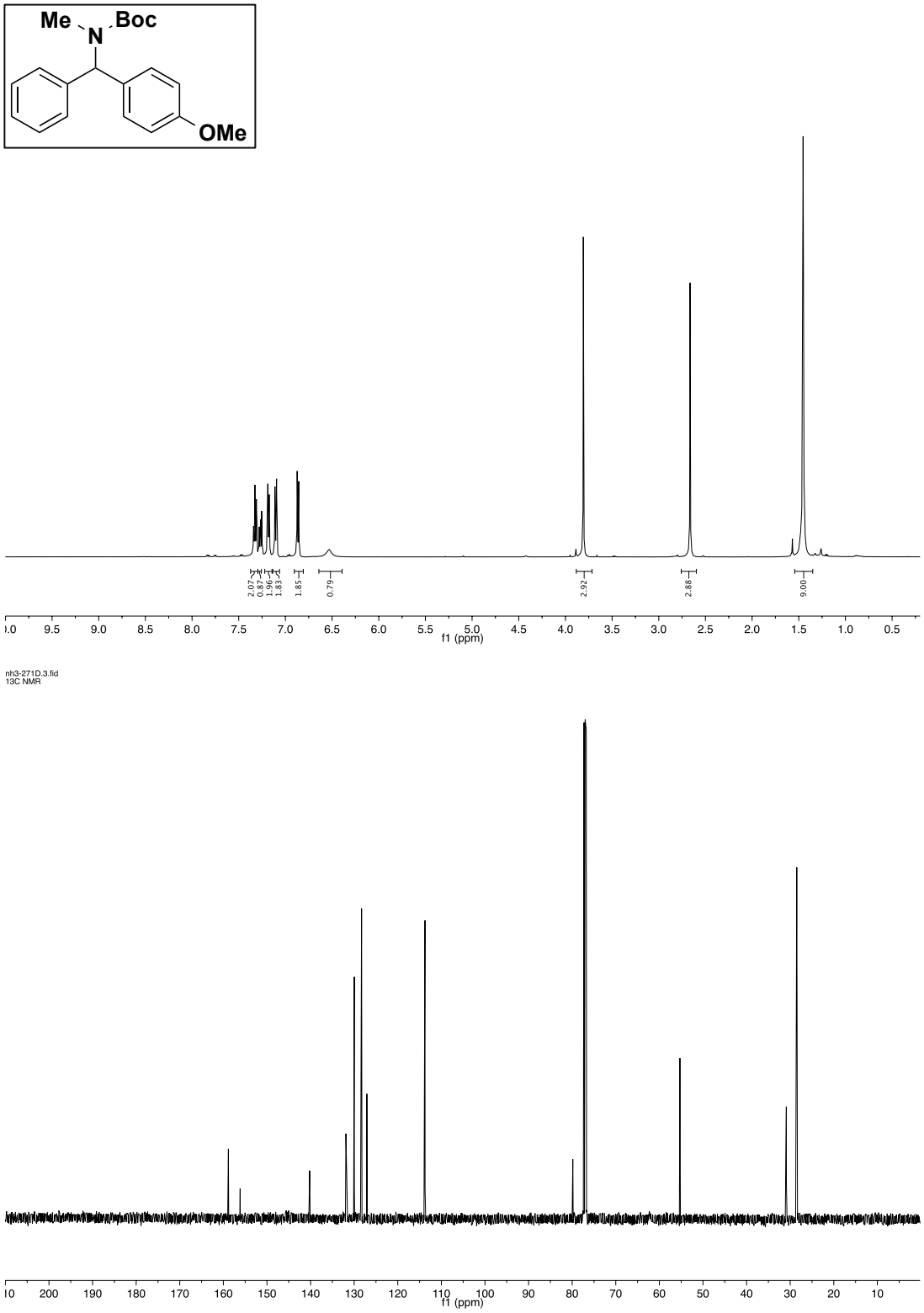


Figure S9 (**4i**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl ((4-methoxyphenyl)(phenyl)methyl)(methyl)carbamate in $CDCl_3$.

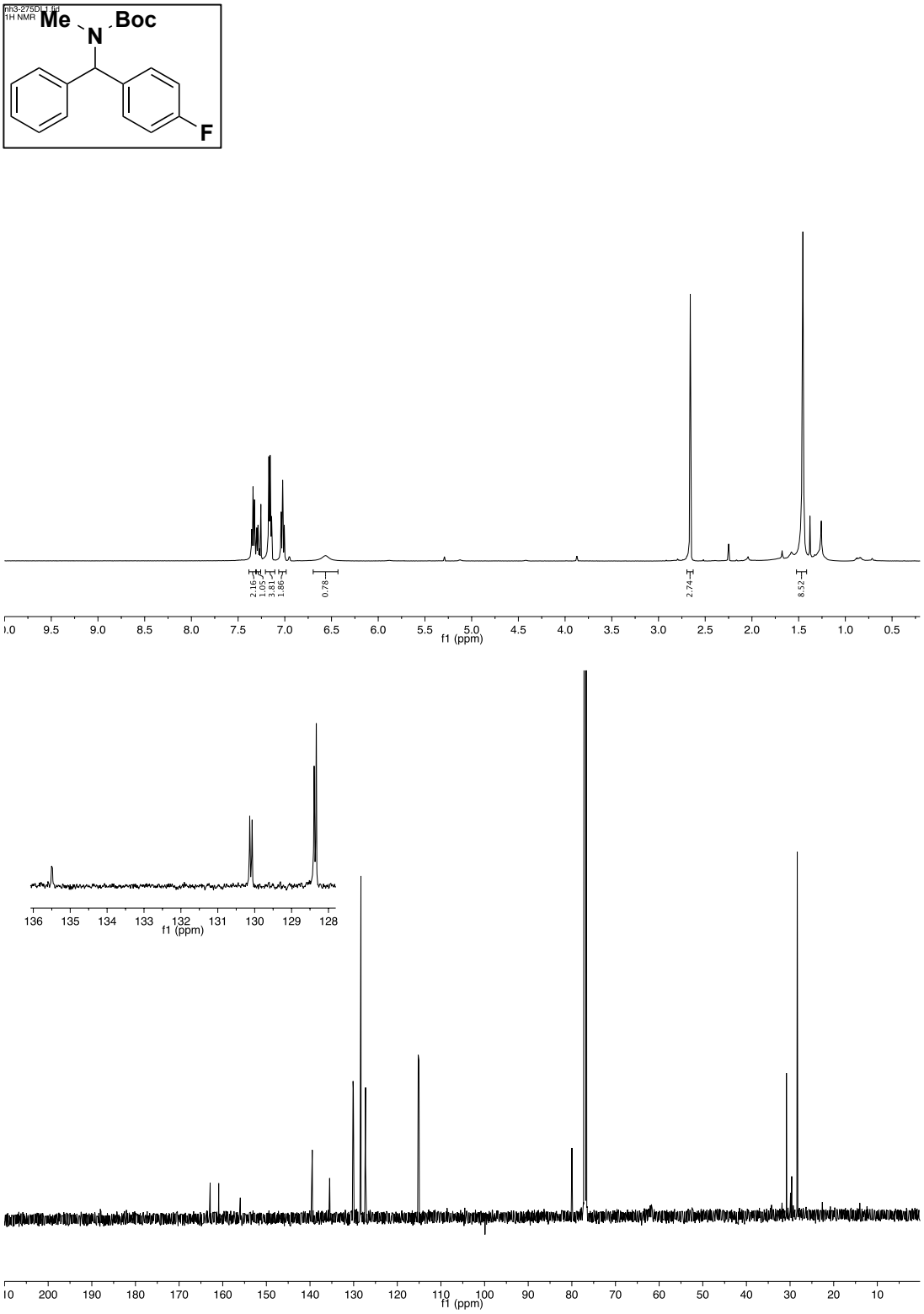


Figure S10 (**4j**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl ((4-fluorophenyl)(phenyl)methyl)(methyl)carbamate in $CDCl_3$.

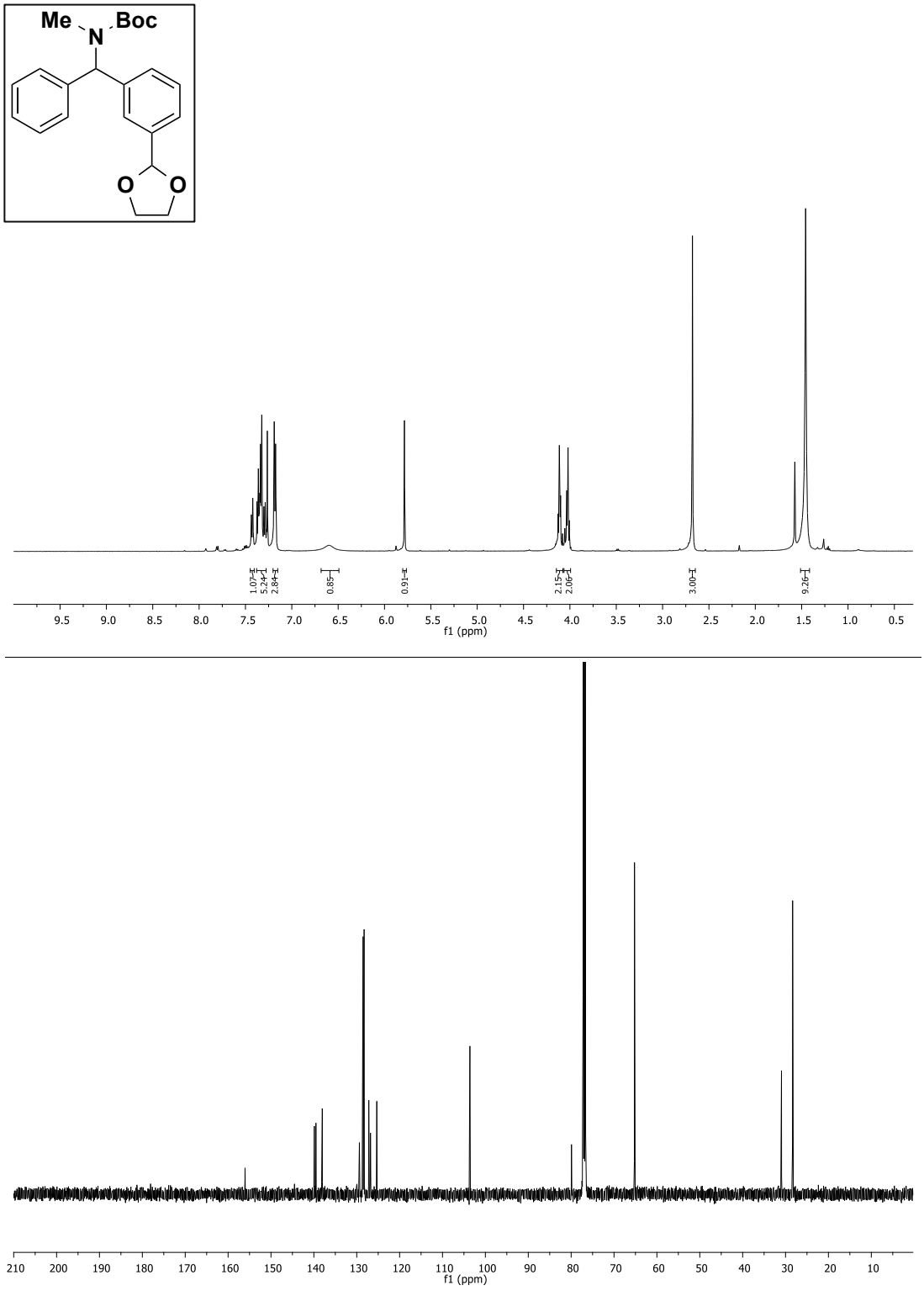


Figure S11 (**4k**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl ((3-(1,3-dioxolan-2-yl)phenyl)(phenyl)methyl)(methyl)carbamate in $CDCl_3$.

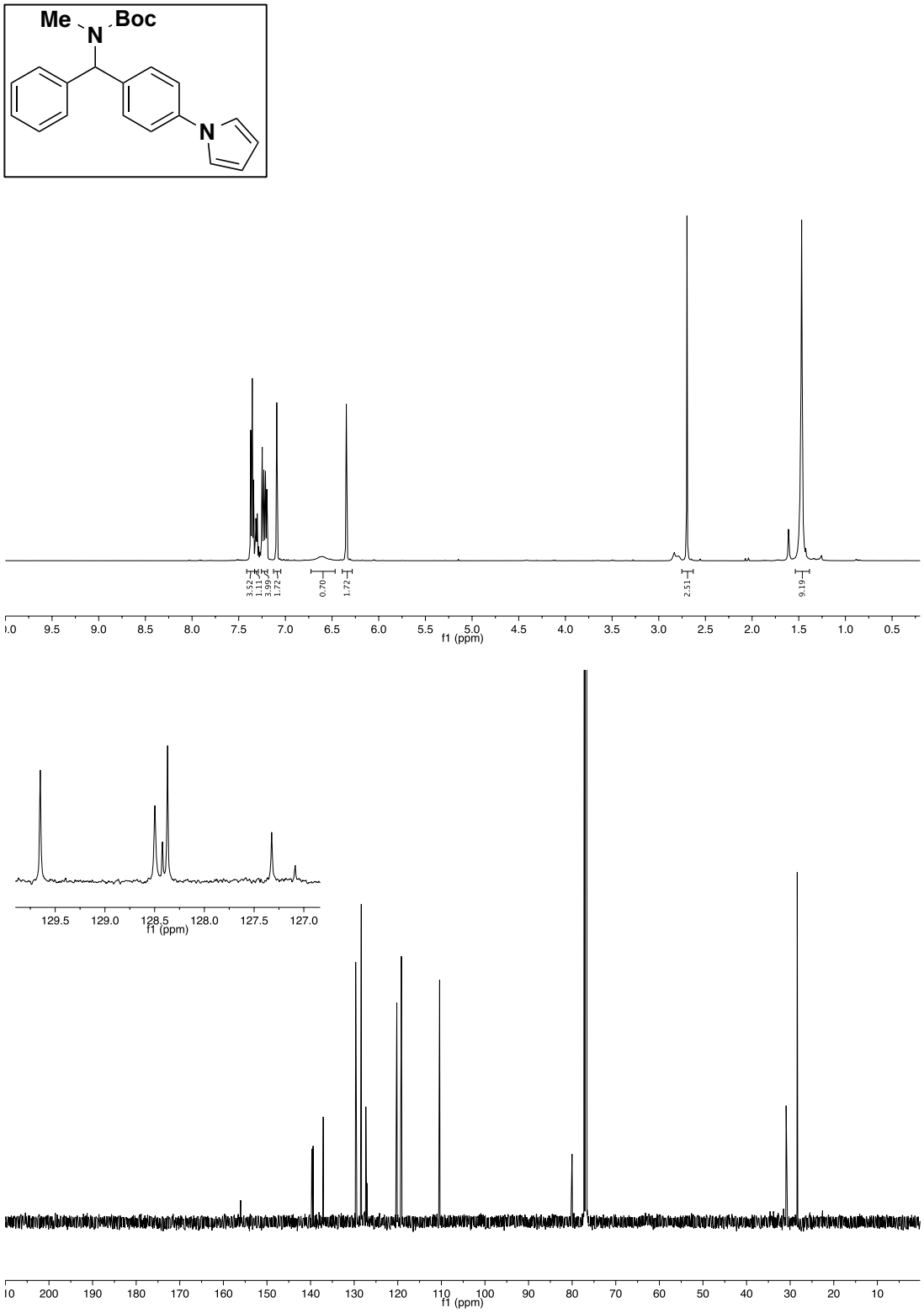


Figure S12 (**4l**). 500 MHz ^{1}H and 125 MHz ^{13}C{^{1}H} NMR of *tert*-butyl ((4-(1*H*-pyrrol-1-yl)phenyl)(phenyl)methyl)(methyl)carbamate in $CDCl_3$.

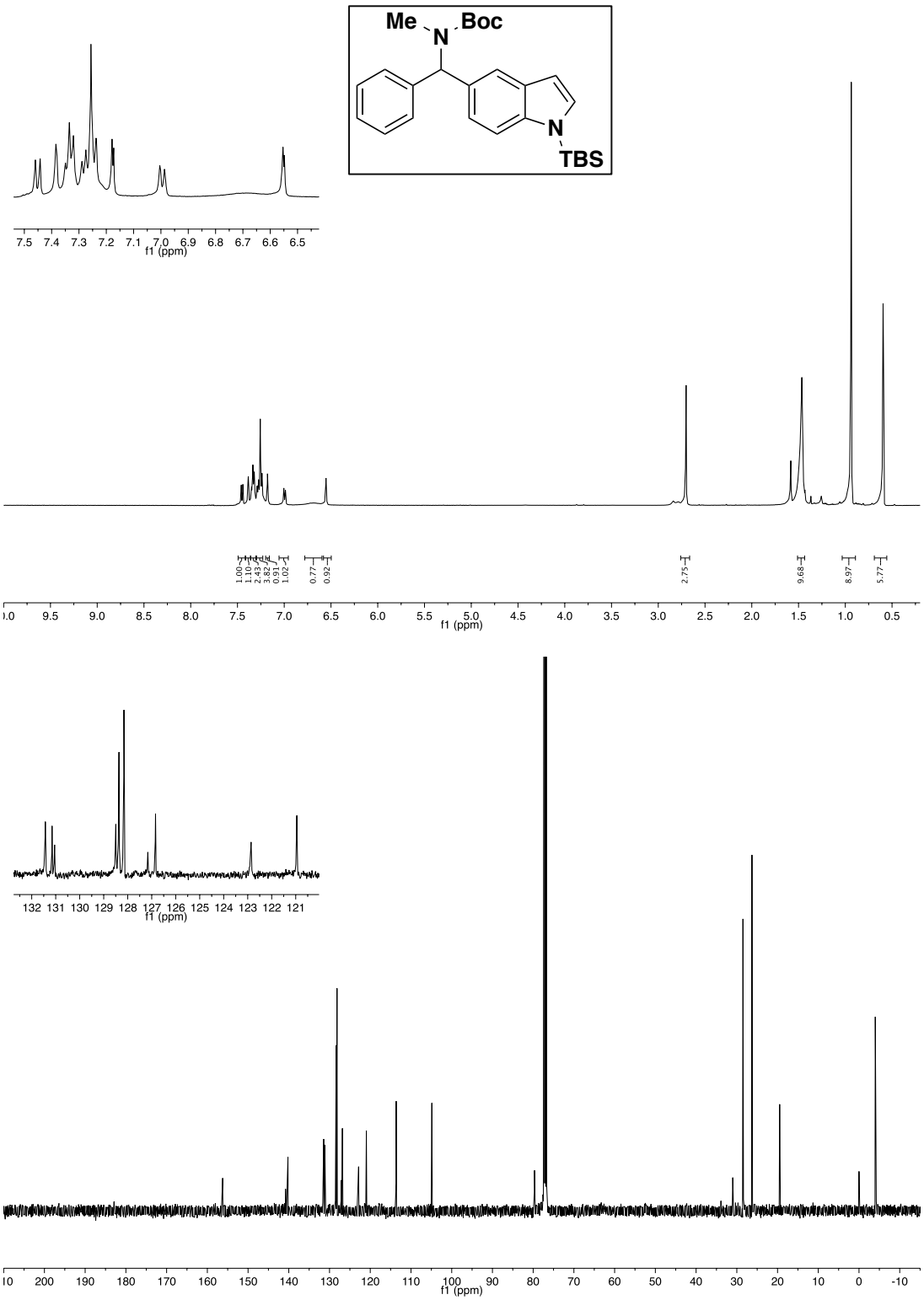


Figure S13 (**4m**). 500 MHz ^{1}H and 125 MHz ^{13}C{H} NMR of *tert*-butyl ((1-(*tert*-butyldimethylsilyl)-1*H*-indol-5-yl)(phenyl)methyl)(methyl)carbamate in $CDCl_3$.

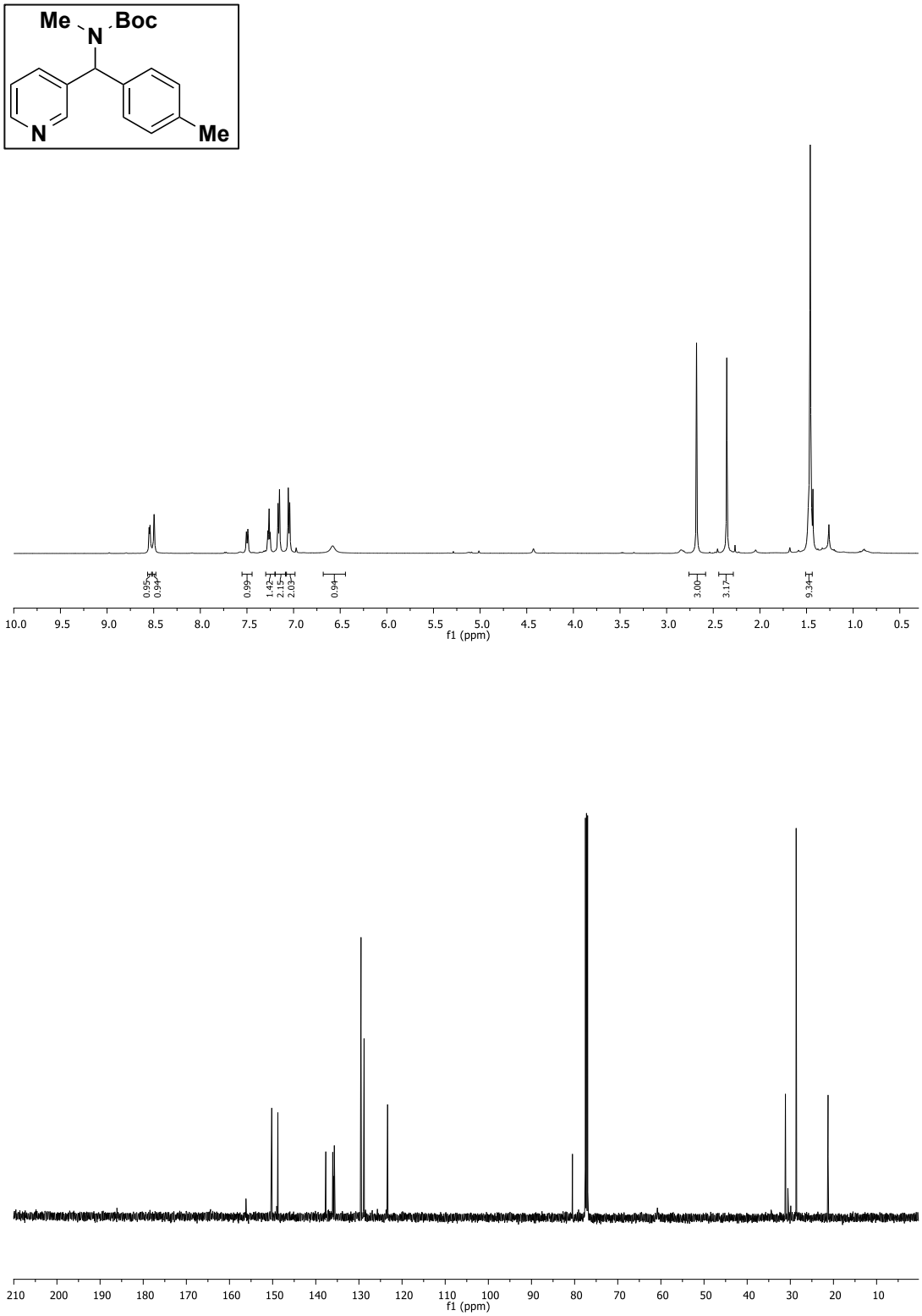


Figure S14 (**4n**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl methyl(pyridin-3-yl(*p*-tolyl)methyl)carbamate in $CDCl_3$.

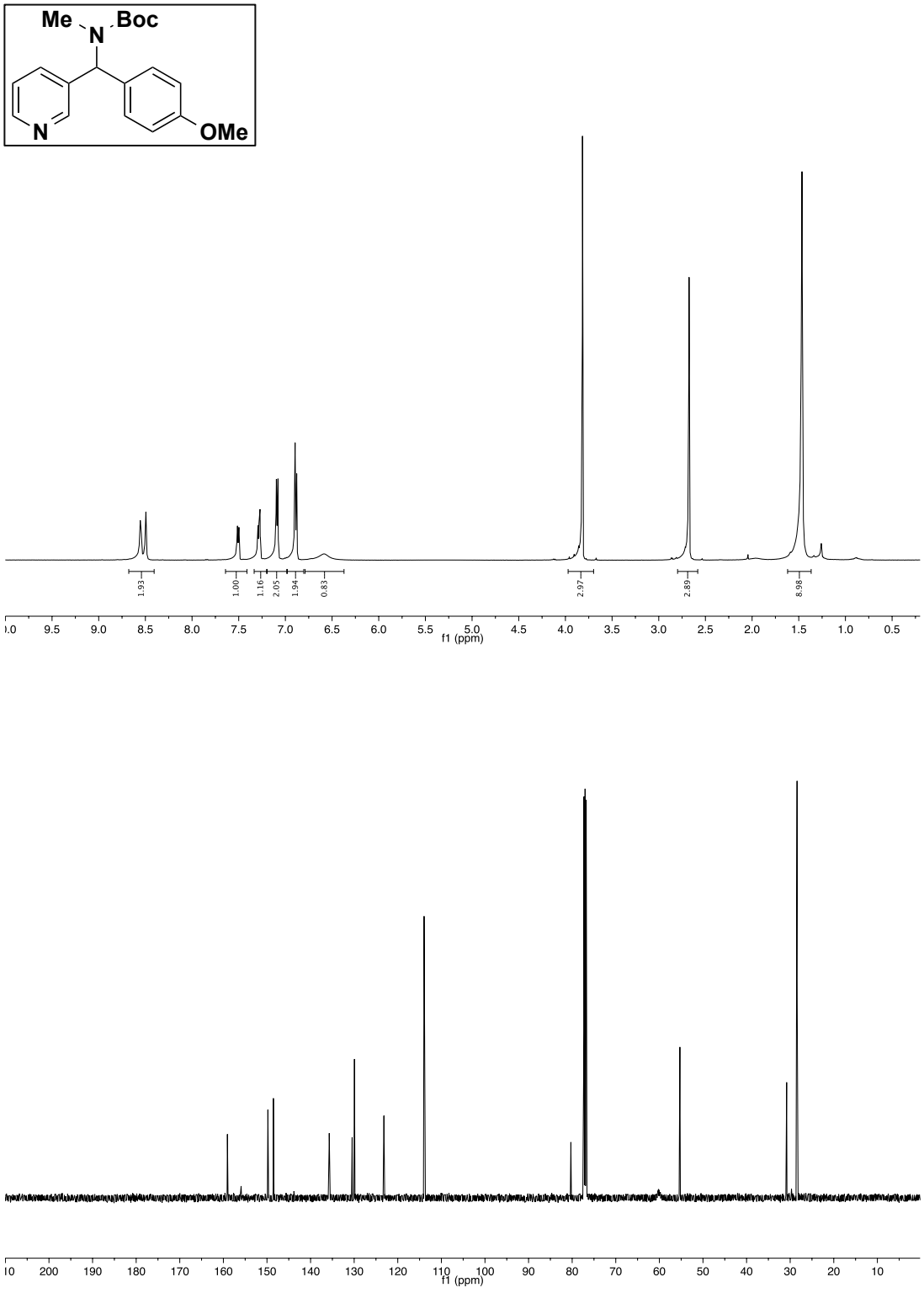


Figure S15 (**4o**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl ((4-methoxyphenyl)(pyridin-3-yl)methyl)(methyl)carbamate in $CDCl_3$.

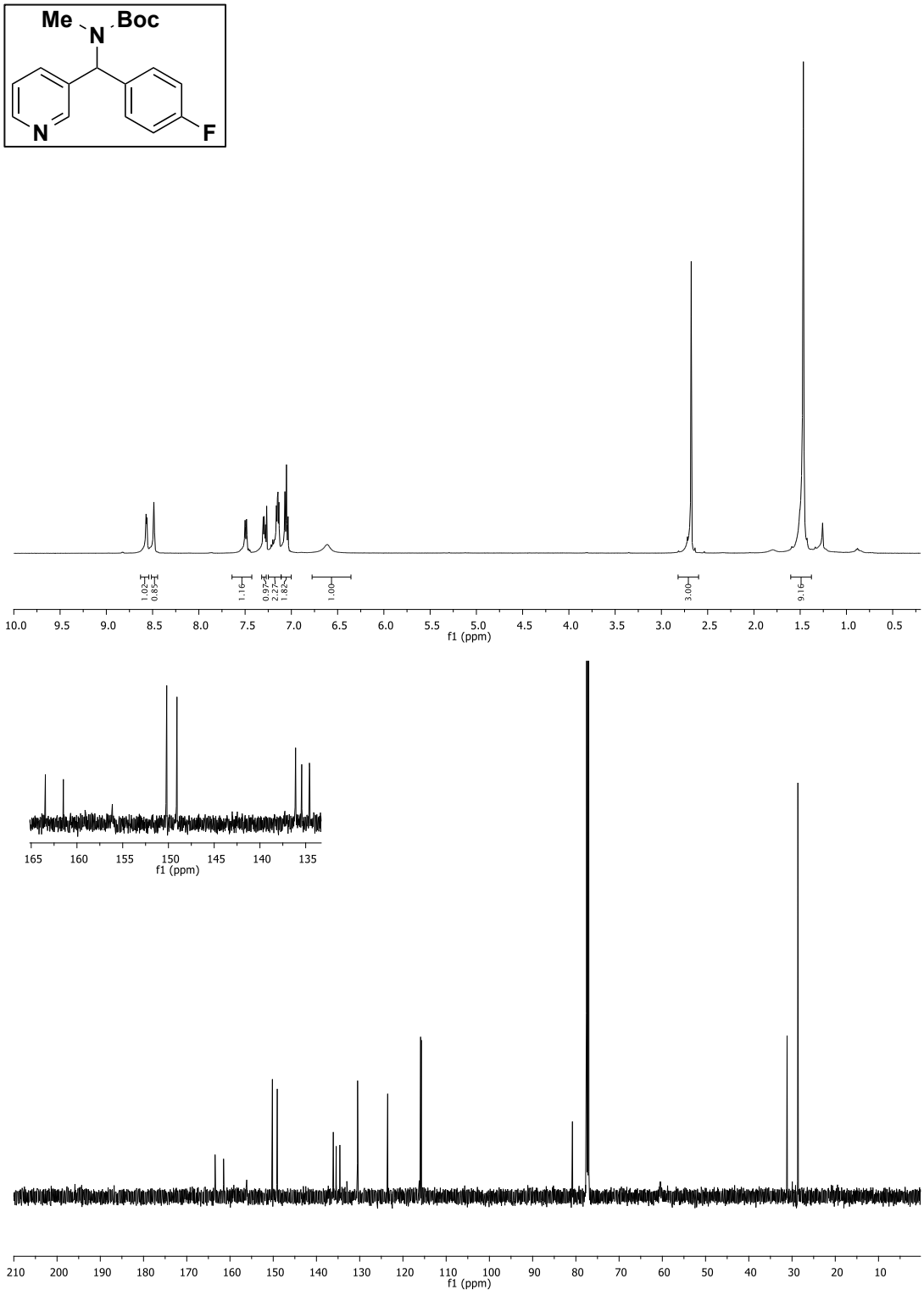


Figure S16 (**4p**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl ((4-fluorophenyl)(pyridin-3-yl)methyl)(methyl)carbamate in $CDCl_3$.

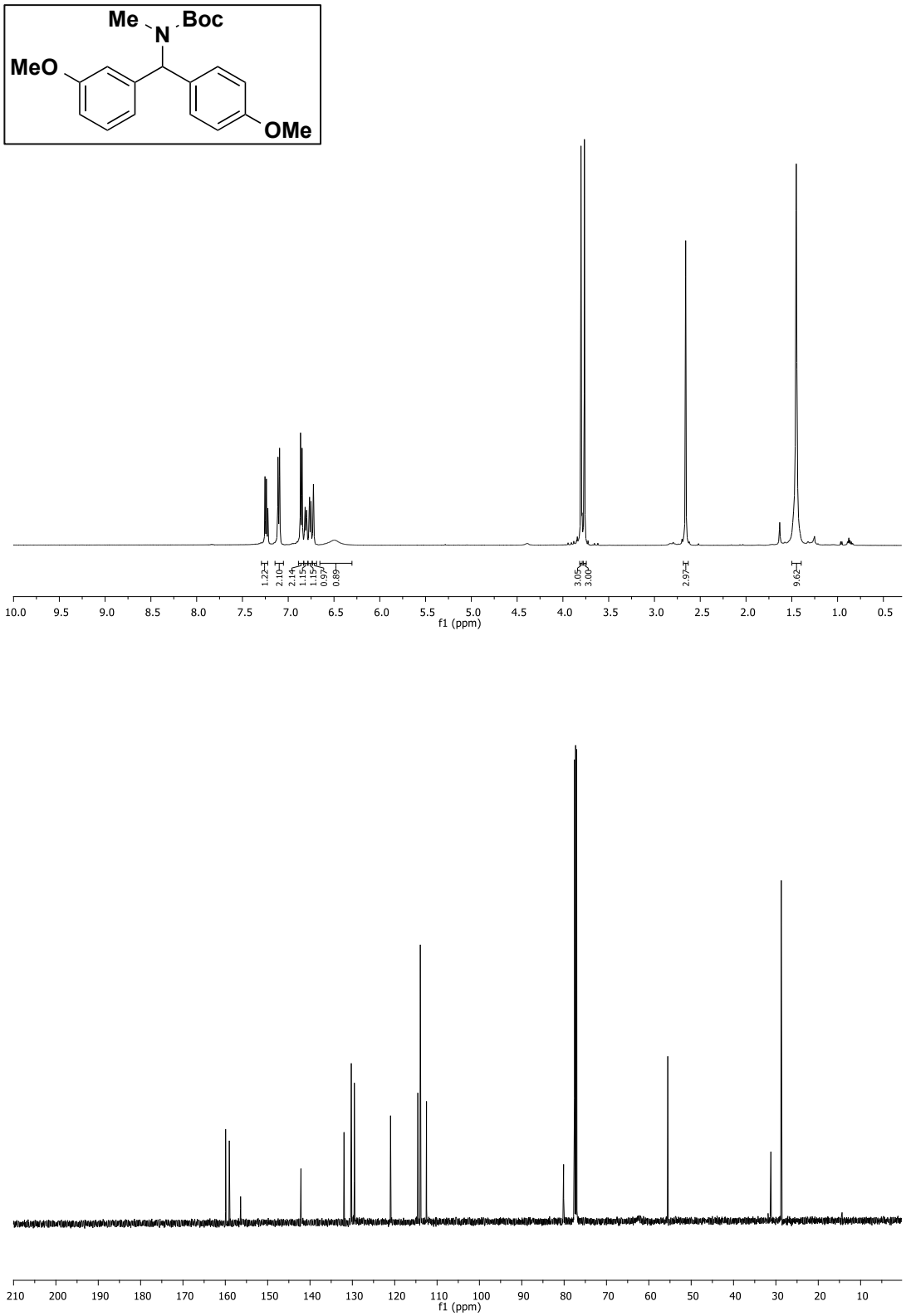


Figure S17 (**4q**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl ((3-methoxyphenyl)(4-methoxyphenyl)methyl)(methyl)carbamate in $CDCl_3$.

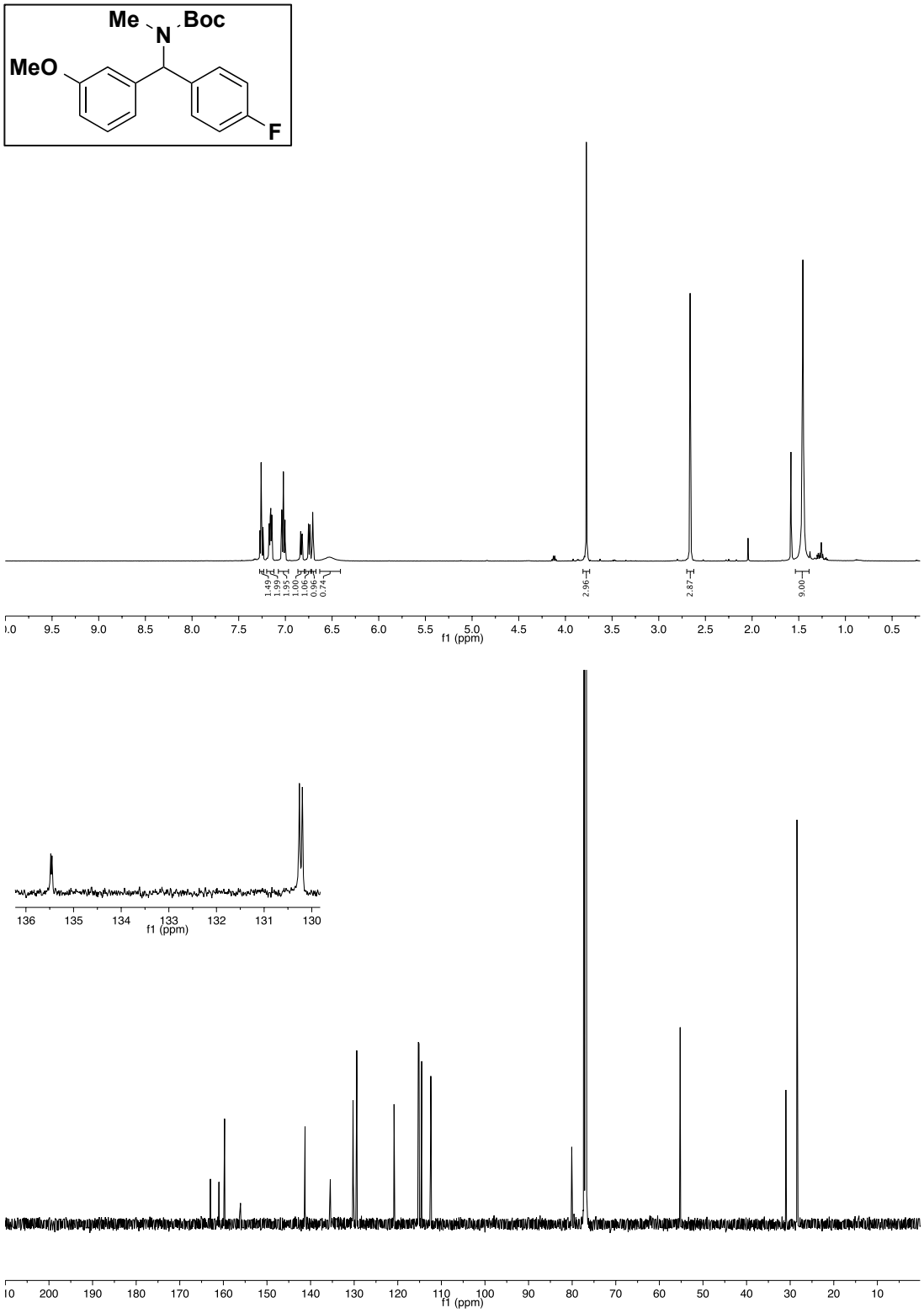


Figure S18 (**4r**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl ((4-fluorophenyl)(3-methoxyphenyl)methyl)(methyl)carbamate in $CDCl_3$.

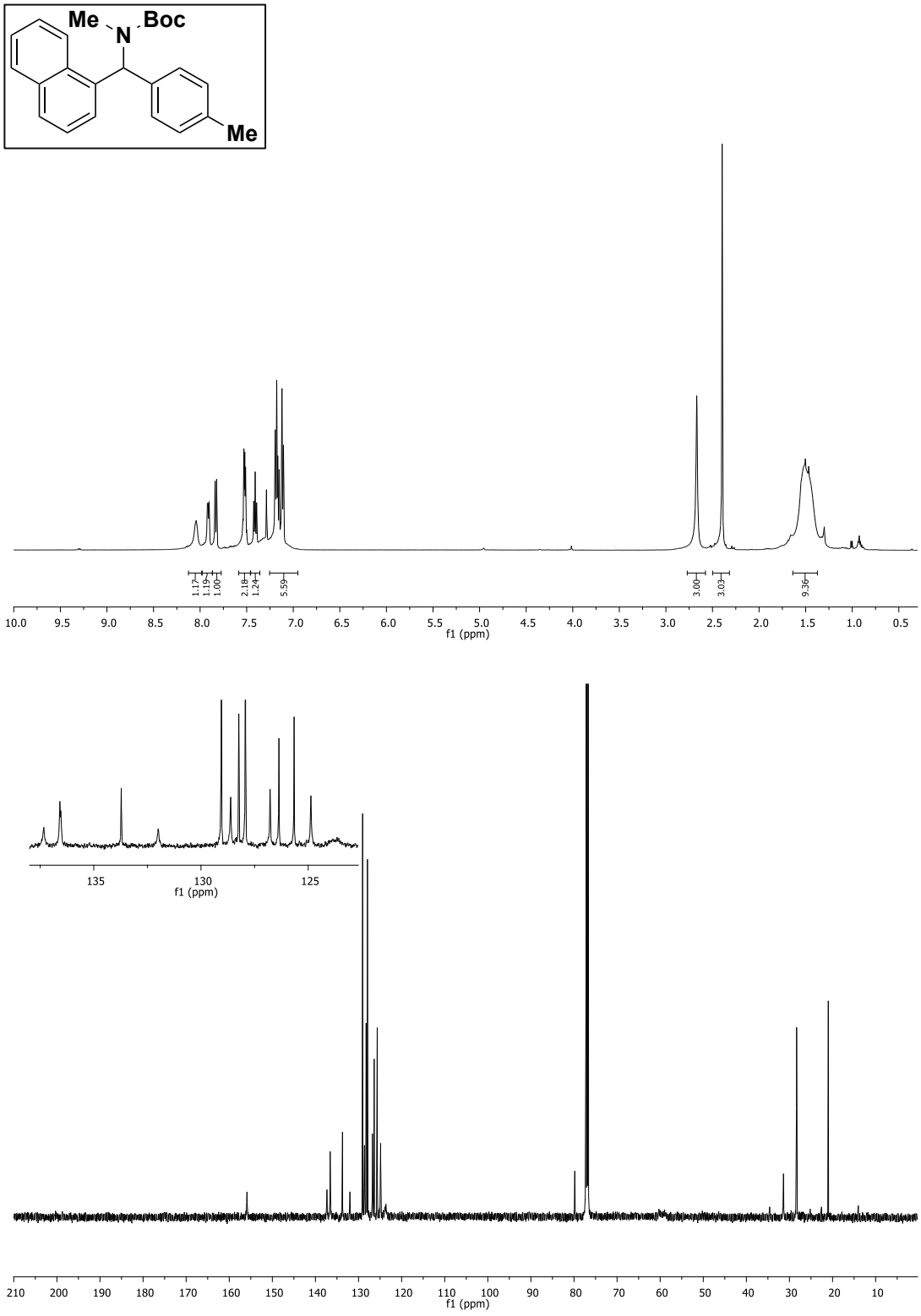


Figure S19 (**4s**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl methyl(naphthalen-2-yl(*p*-tolyl)methyl)carbamate in $CDCl_3$.

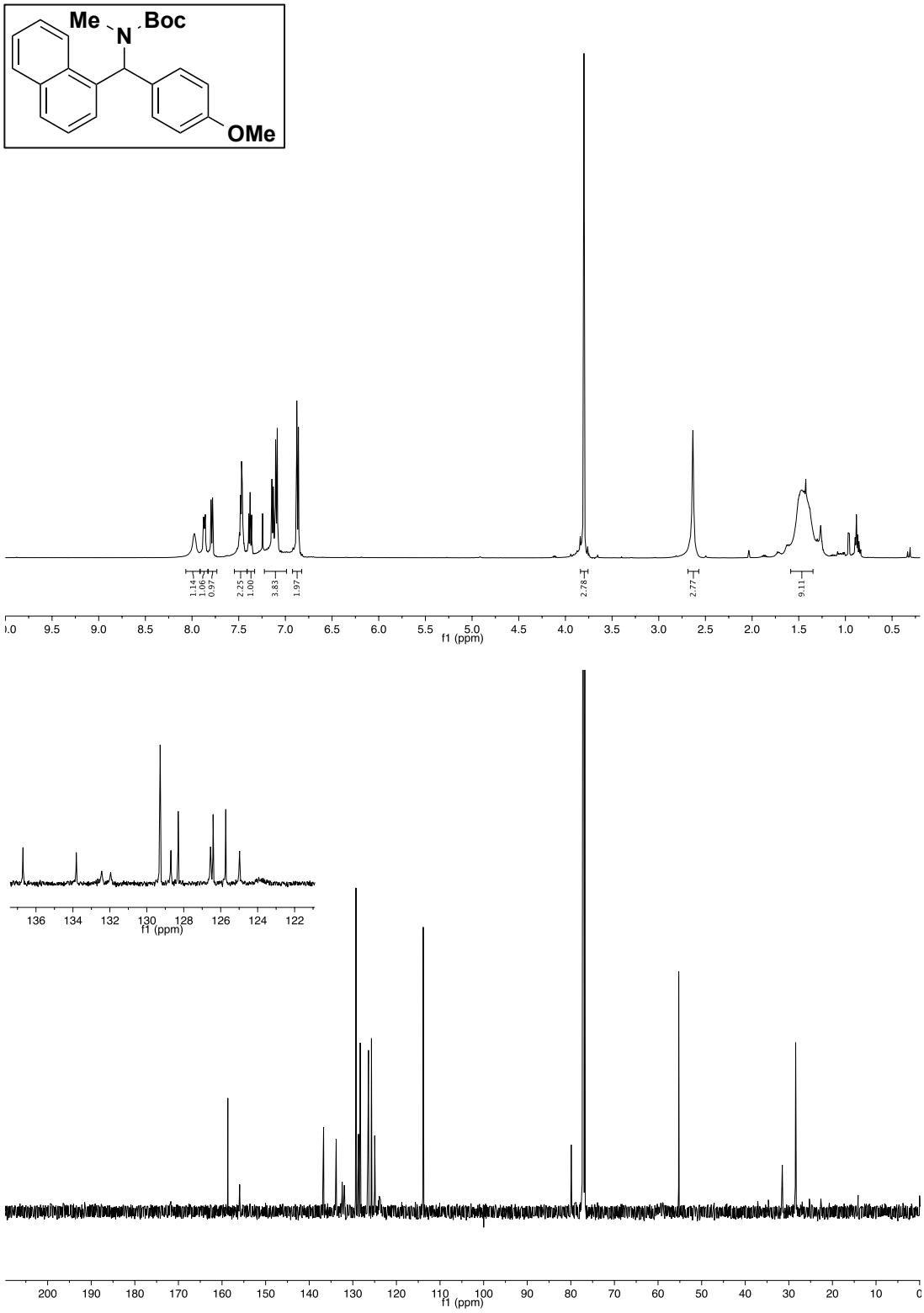


Figure S20 (**4s**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl ((4-methoxyphenyl)(naphthalen-2-yl)methyl)(methyl)carbamate in $CDCl_3$.

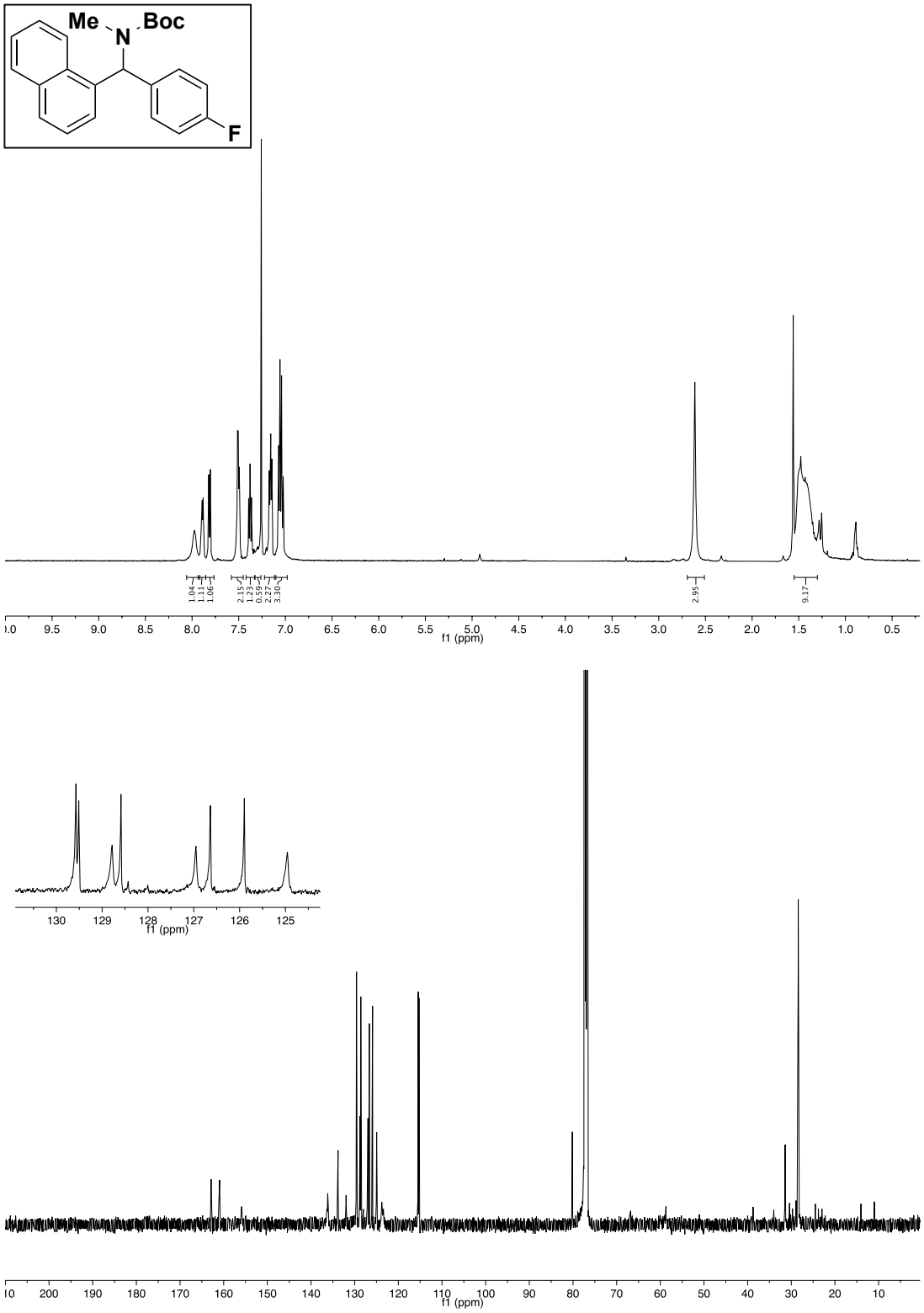


Figure S21 (**4u**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl ((4-fluorophenyl)(naphthalen-2-yl)methyl)(methyl)carbamate in $CDCl_3$

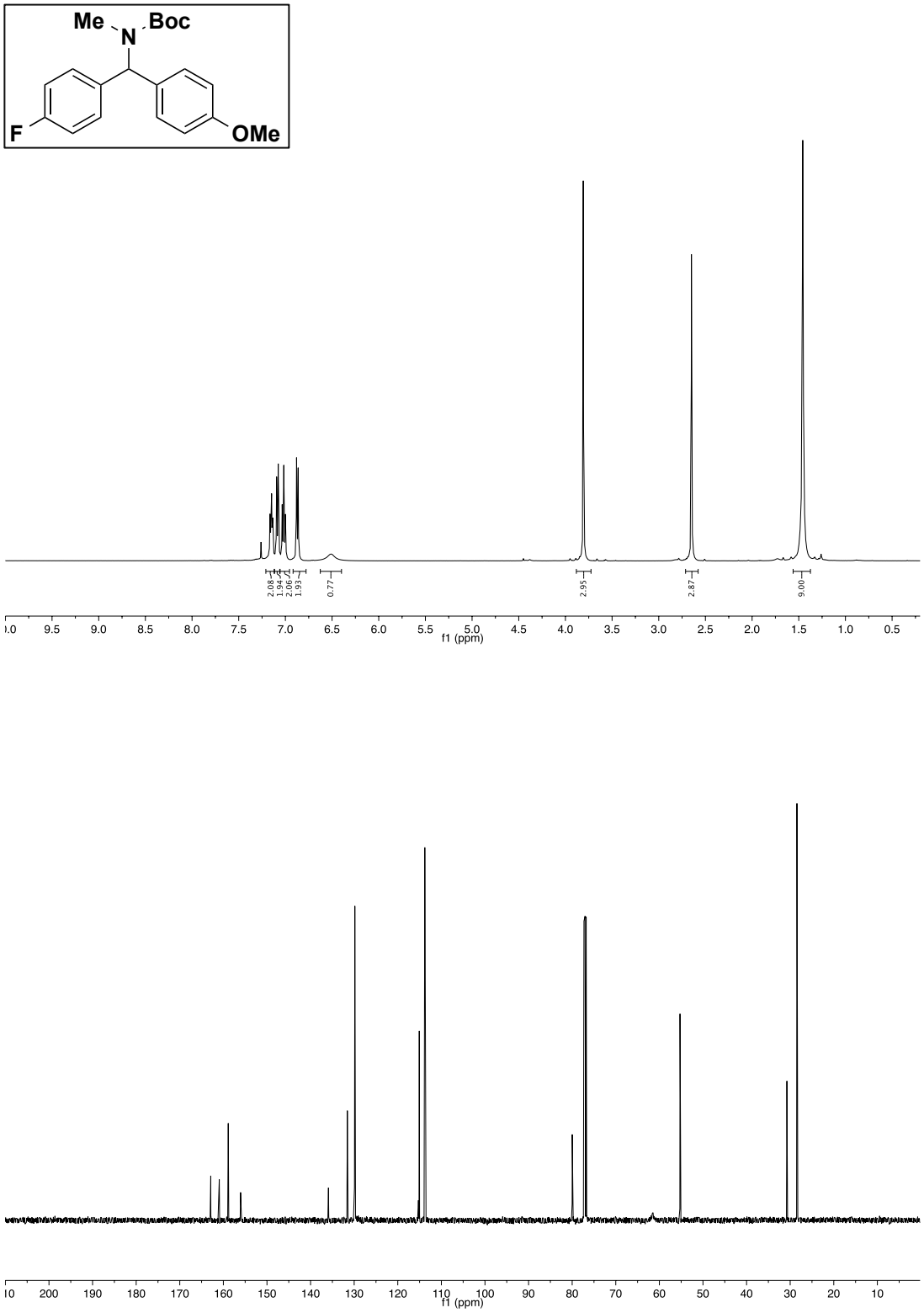


Figure S22 (**4v**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl ((4-fluorophenyl)(4-methoxyphenyl)methyl)(methyl)carbamate in $CDCl_3$.

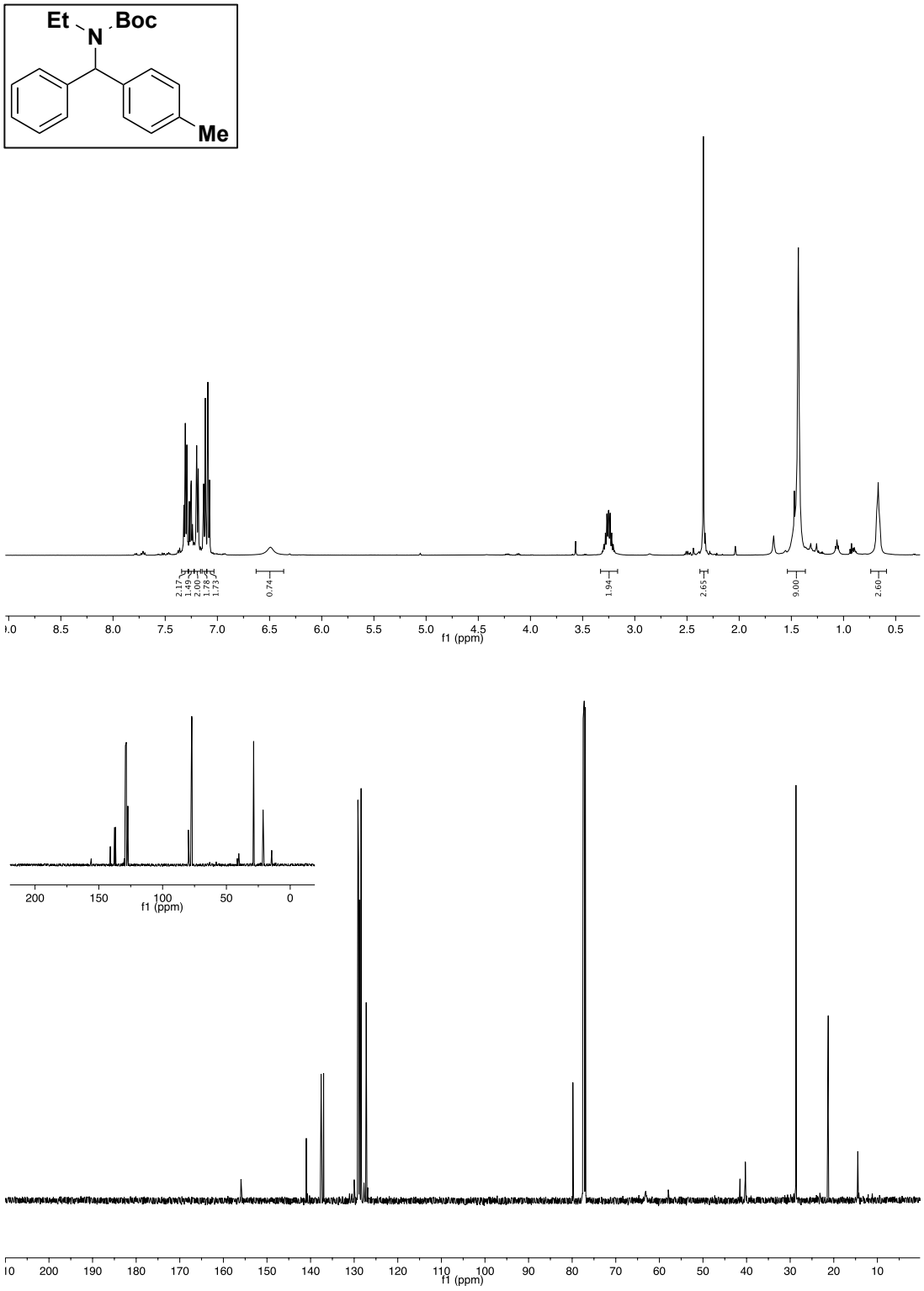


Figure S23 (**4w**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl ethyl(phenyl(*p*-tolyl)methyl)carbamate in $CDCl_3$.

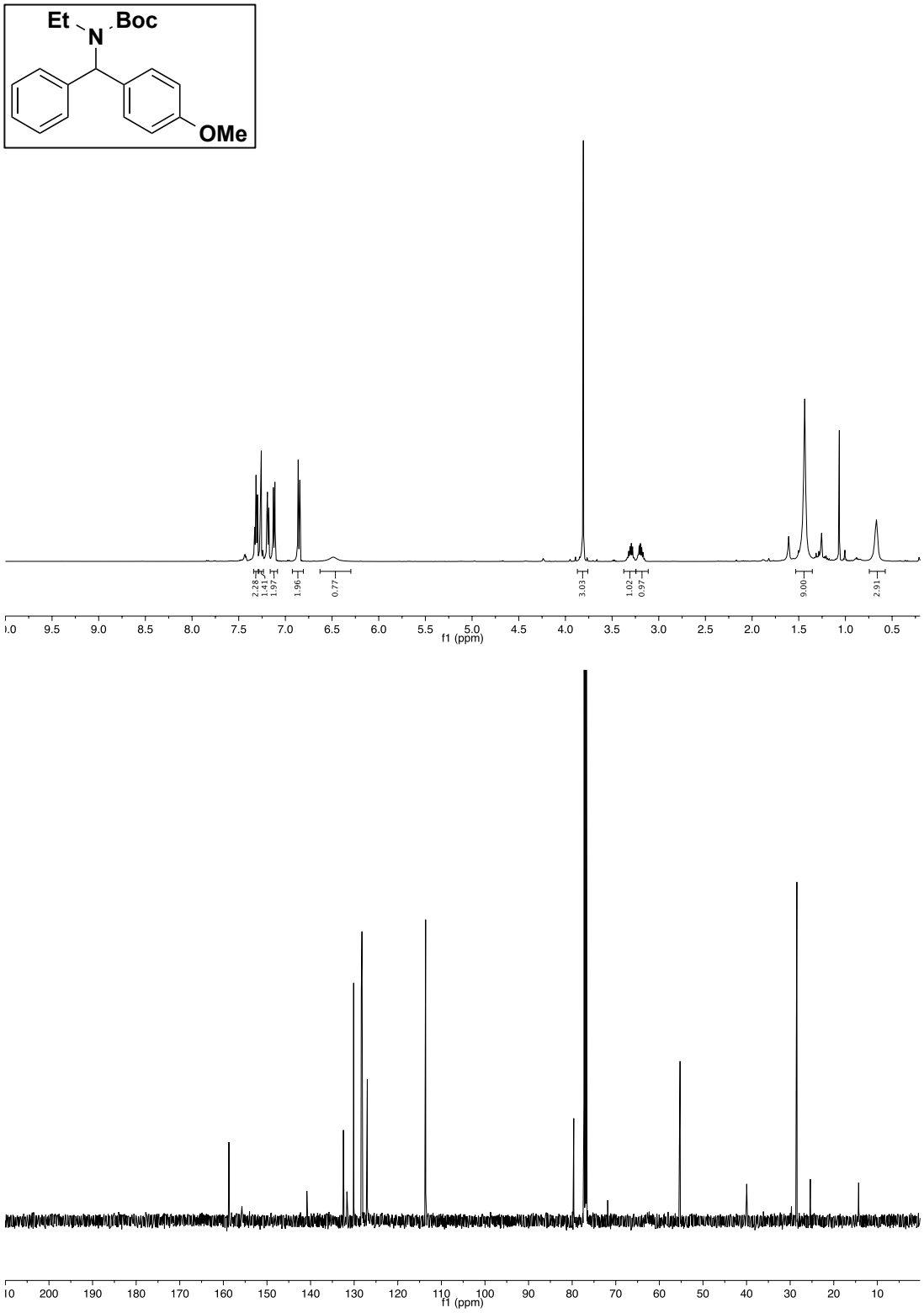


Figure S24 (**4x**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl ethyl((4-methoxyphenyl)(phenyl)methyl)carbamate in $CDCl_3$.

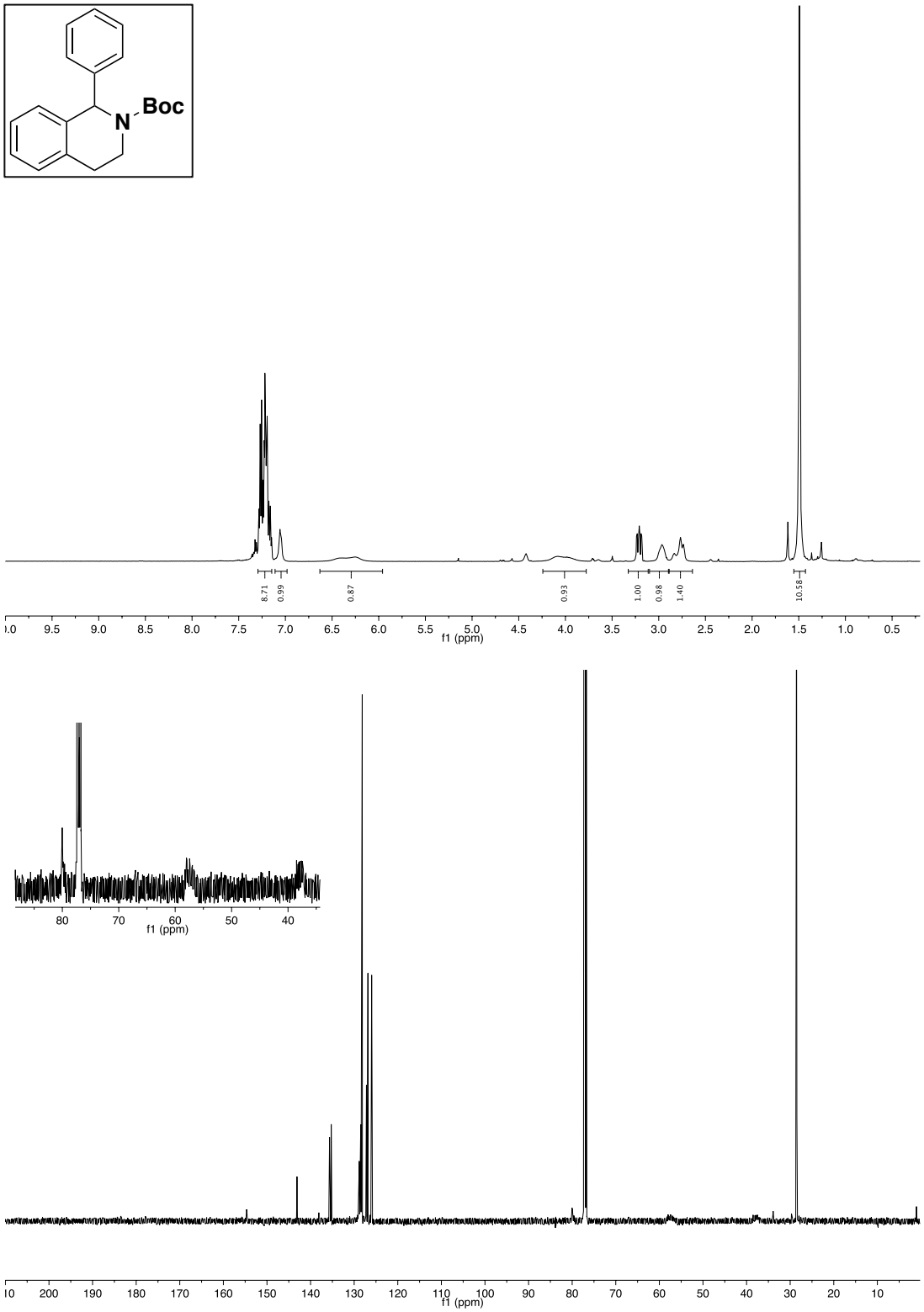


Figure S25 (**4aa**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl 1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate in $CDCl_3$.

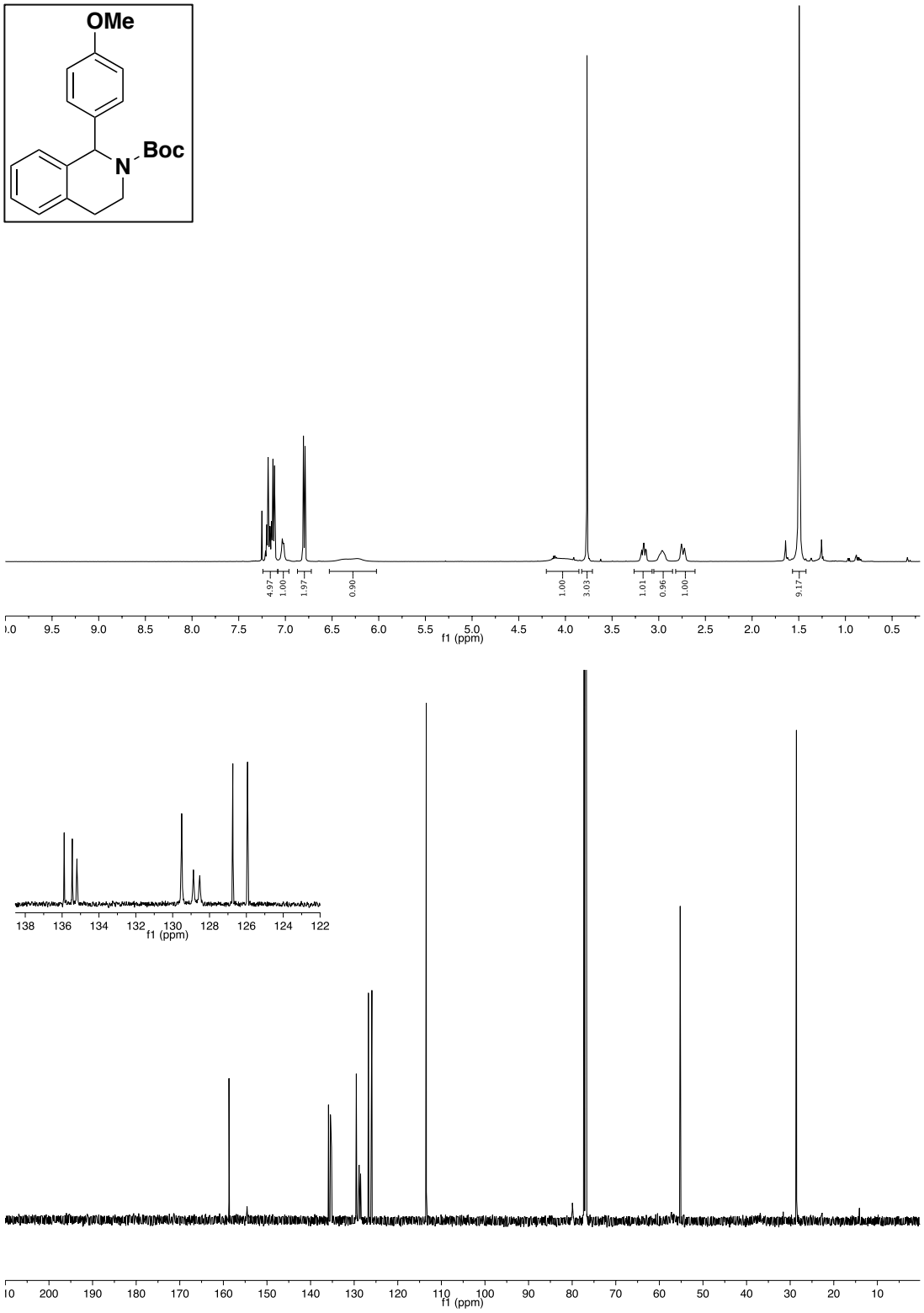


Figure S26 (**4ab**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl 1-(4-methoxyphenyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate in $CDCl_3$.

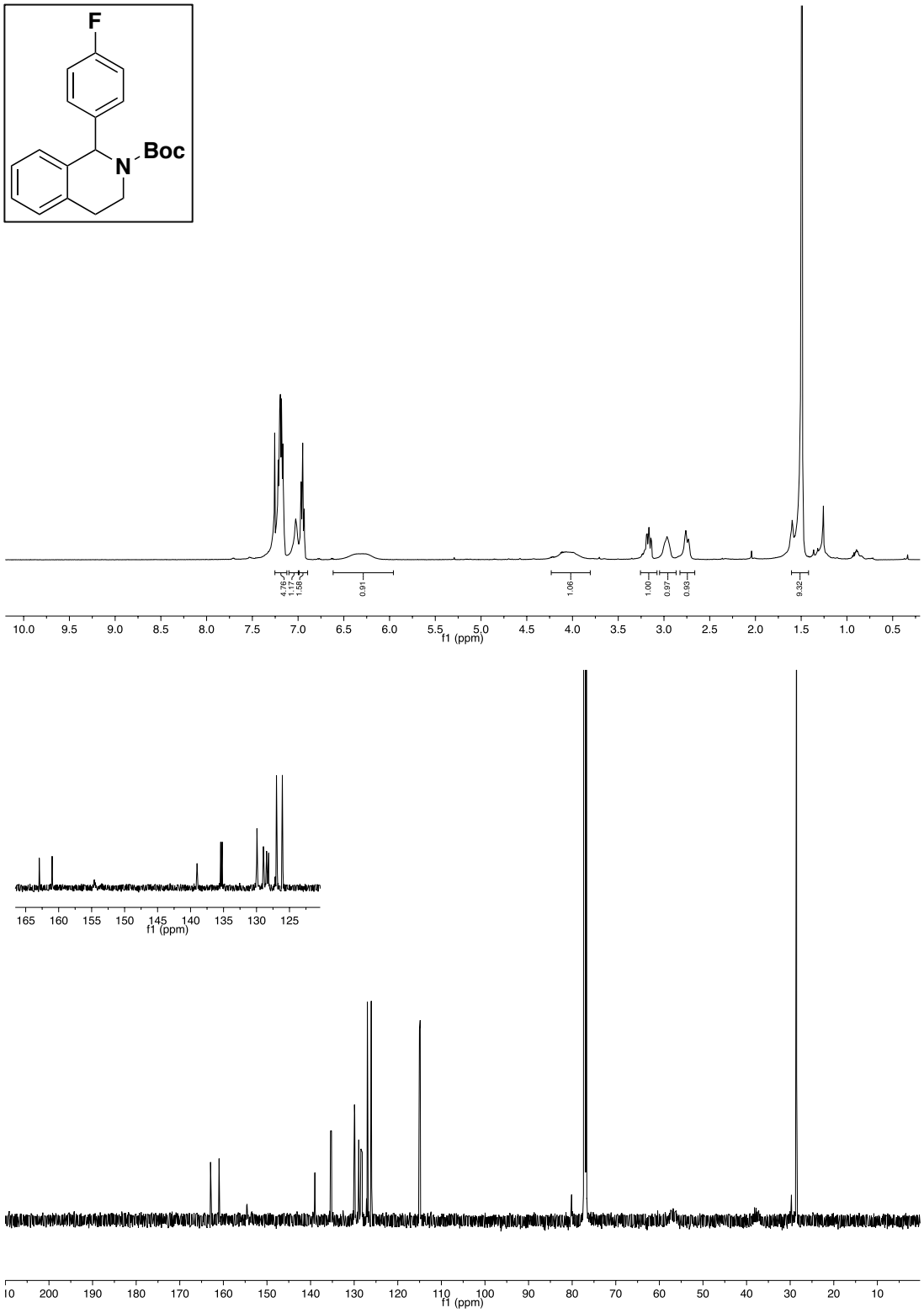


Figure S27 (**4ac**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of *tert*-butyl 1-(4-fluorophenyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate in $CDCl_3$.

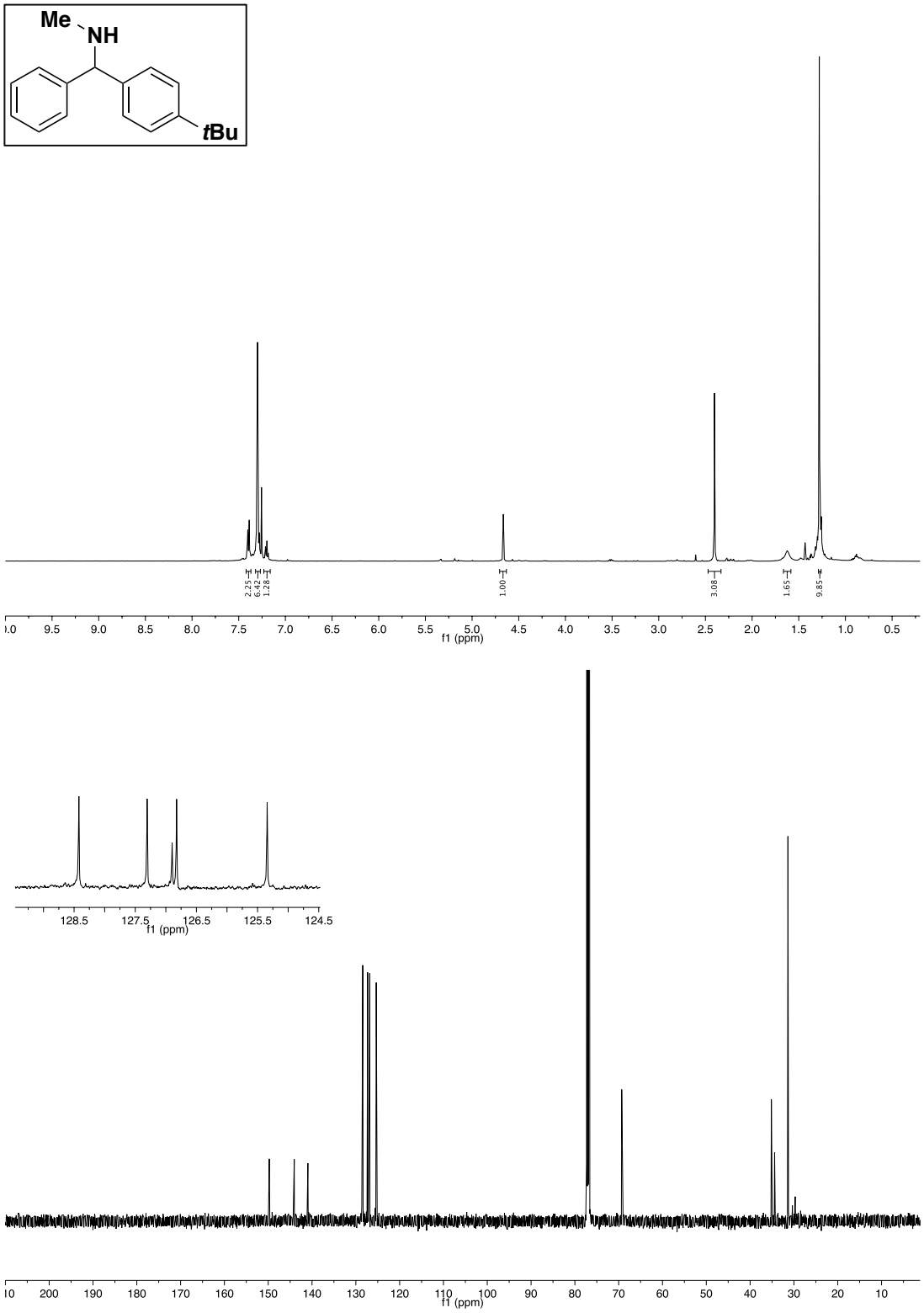


Figure S28 (**5c**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 1-(4-(*tert*-butyl)phenyl)-*N*-methyl-1-phenylmethanamine in $CDCl_3$.

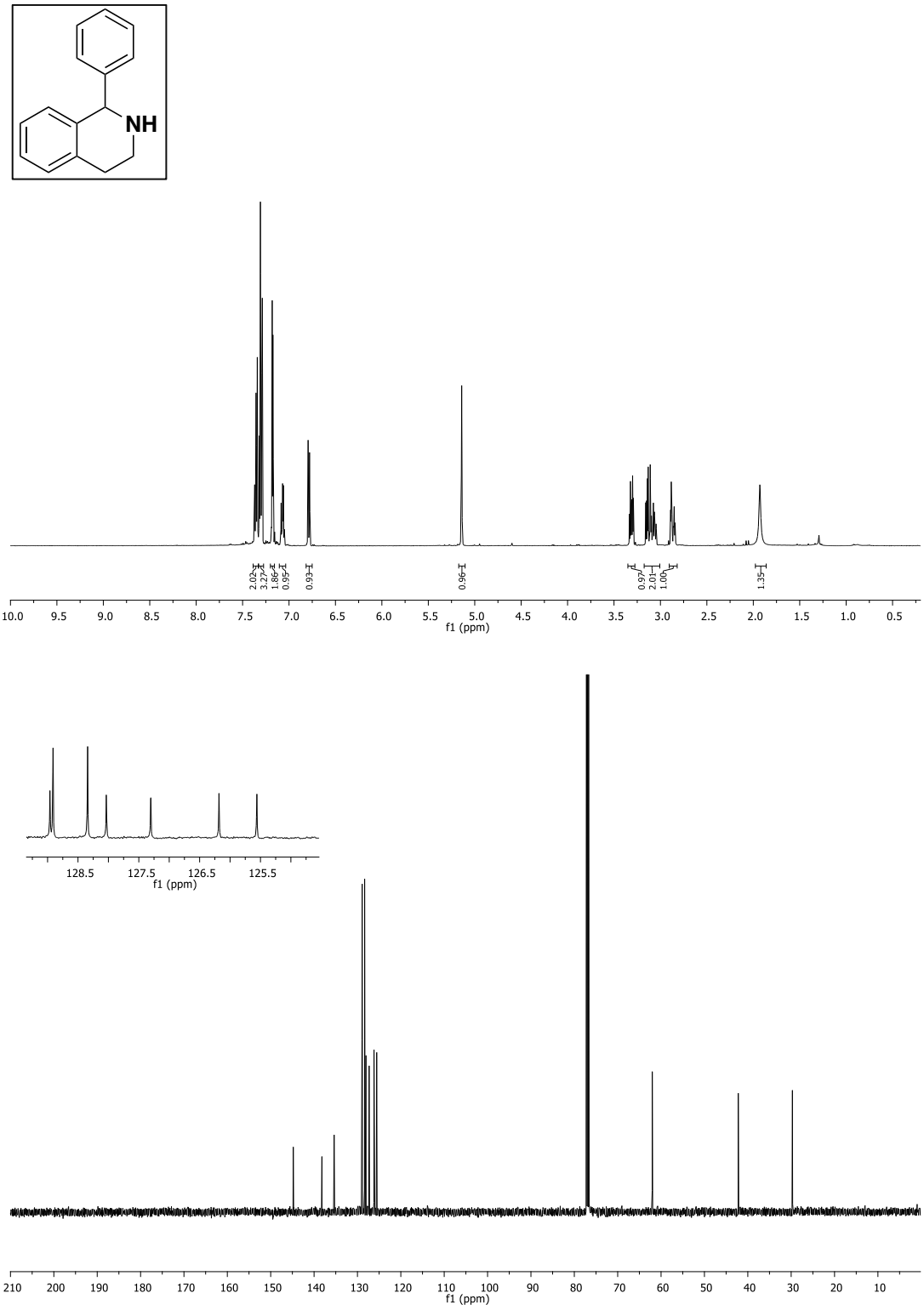
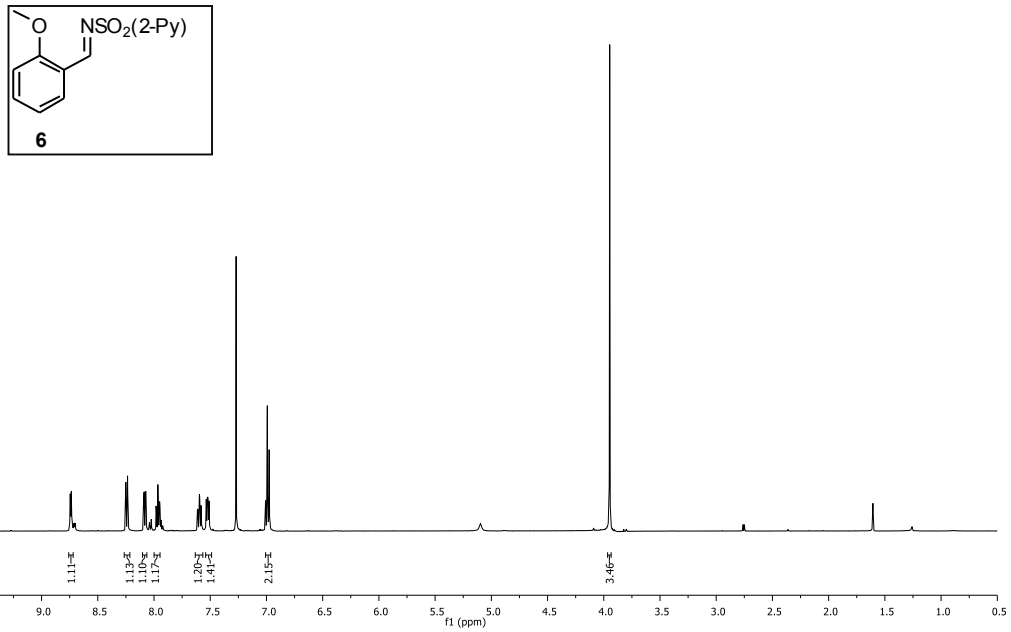
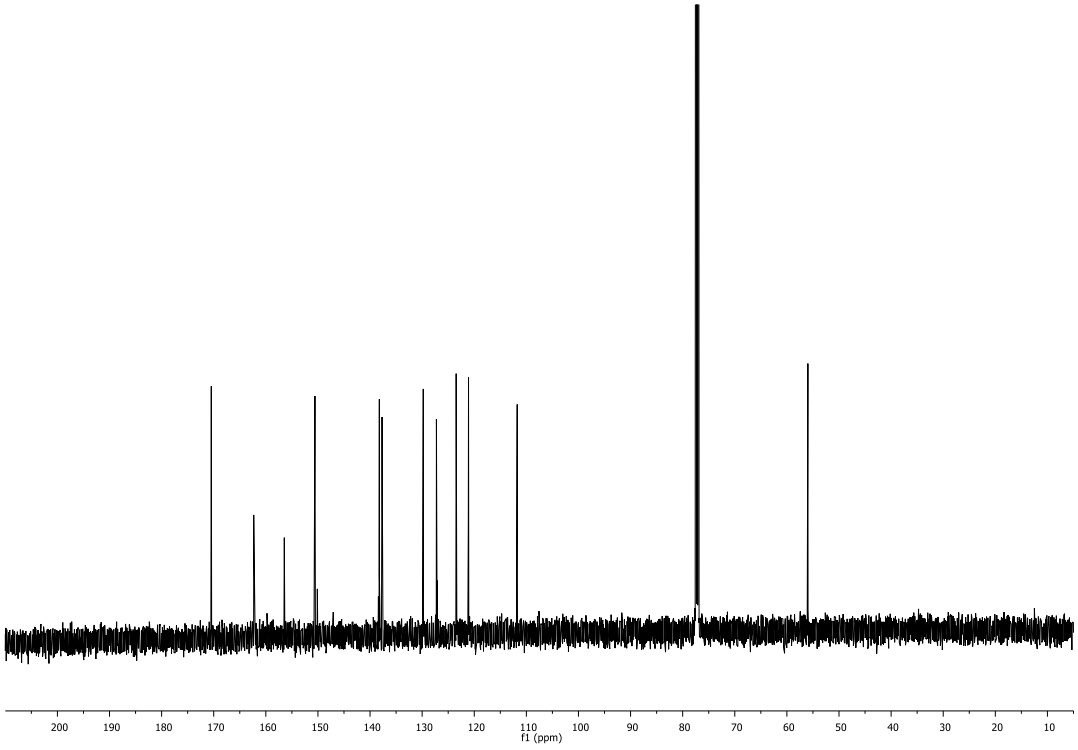
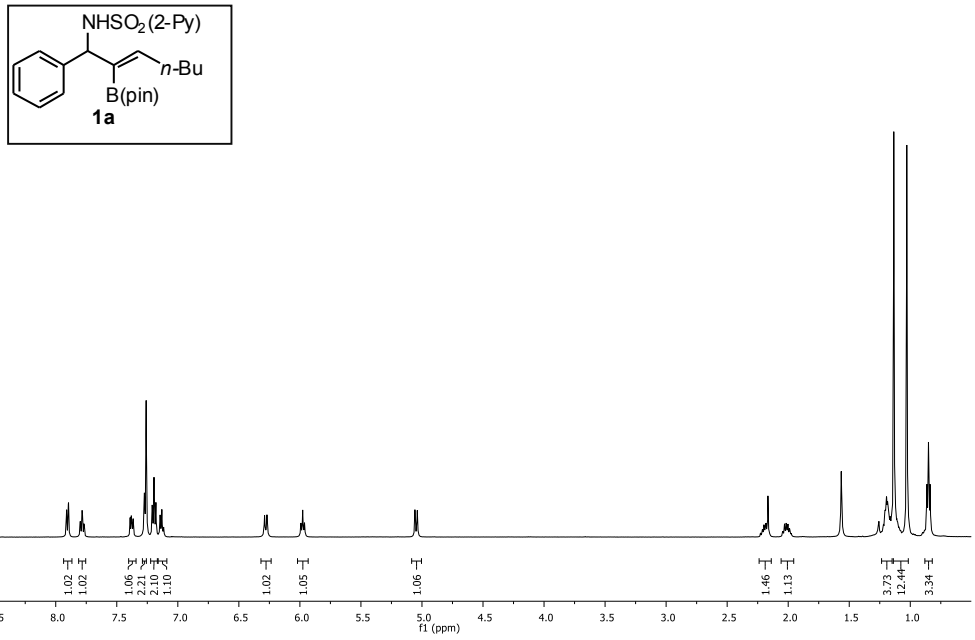


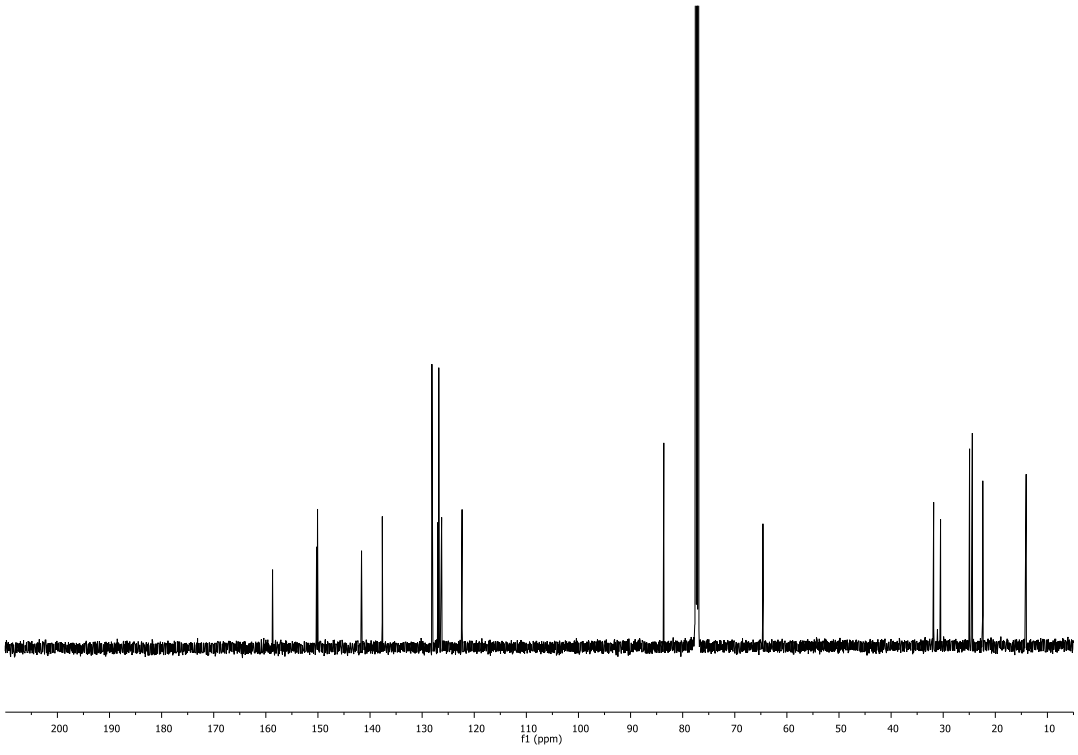
Figure S29 (**5aa**). 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 1-phenyl-1,2,3,4-tetrahydroisoquinoline in $CDCl_3$.

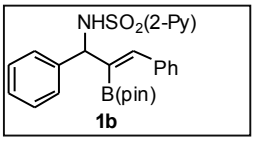
Appendix A1 NMR Spectra Relavant to Chapter 3


O
NSO2(2-Py)
6
1.00
1.11
1.13
1.10
1.17
1.20
1.41
2.15
3.46
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

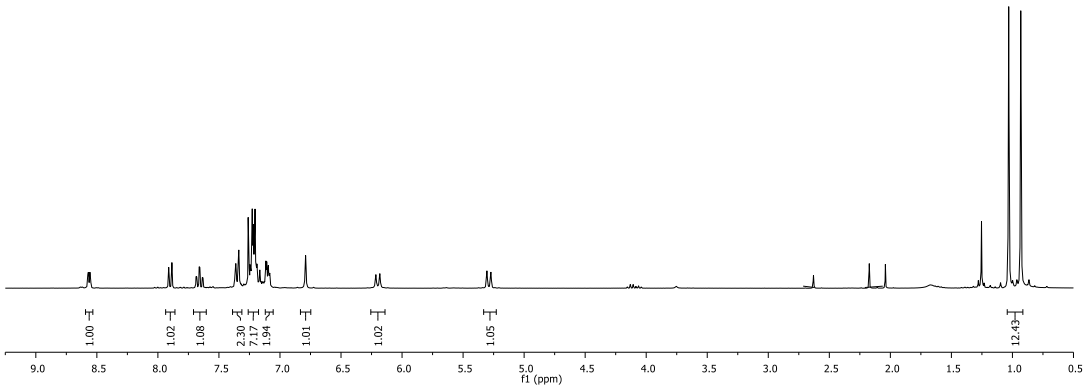

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

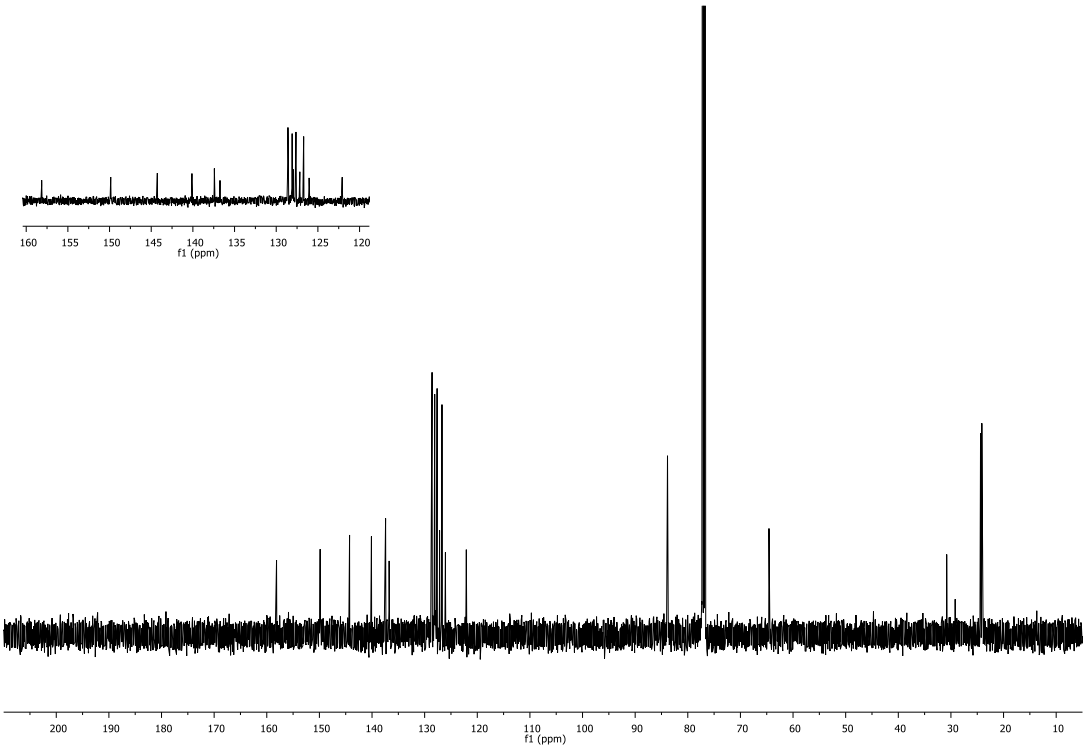

NHSO2(2-Py)
n-Bu
B(pin)
1a
1.00
1.02
1.02
1.06
2.21
2.10
1.10
1.02
1.05
1.06
1.46
1.13
3.73
12.44
3.34
f1 (ppm)

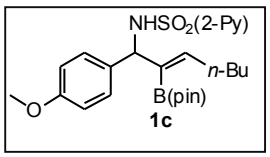

f1 (ppm)


NHSO2(2-Py)
Ph
B(pin)

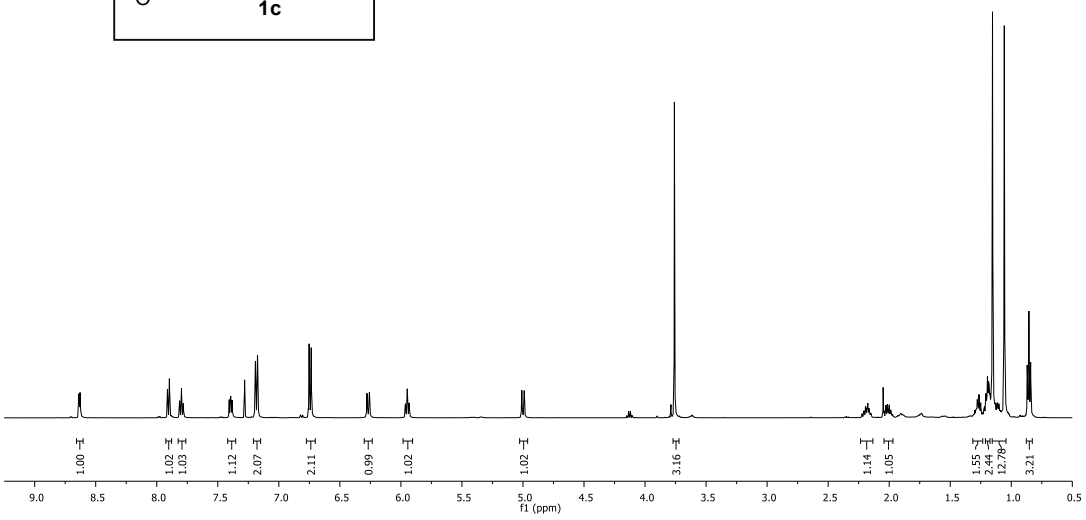
1b

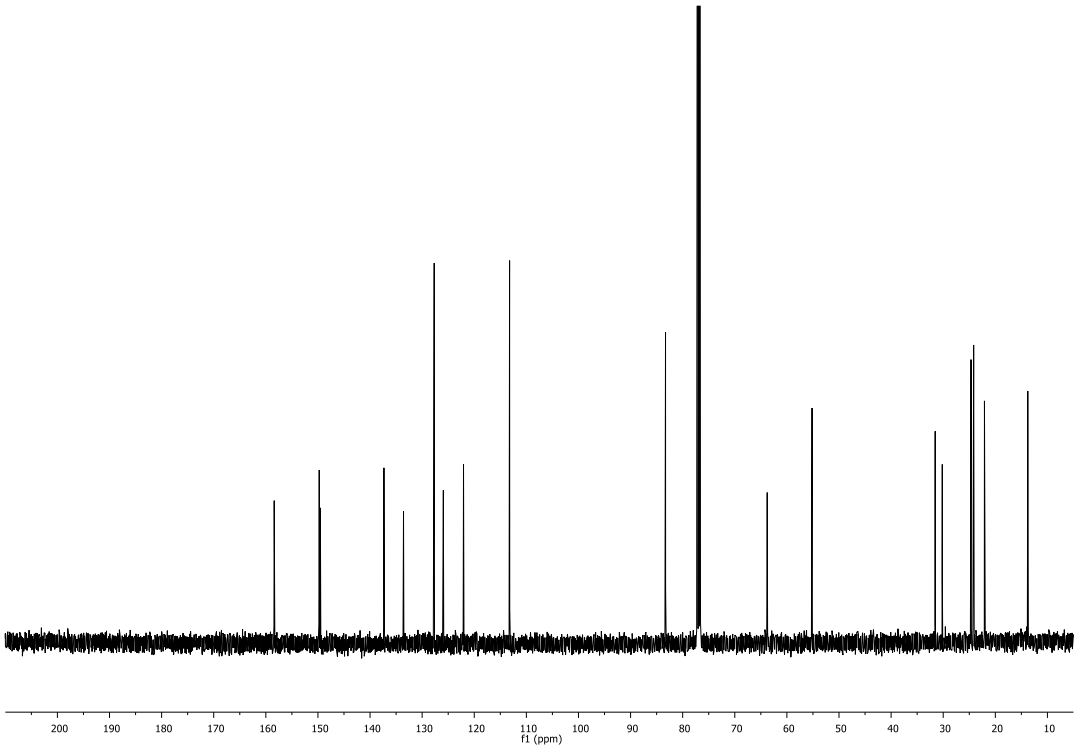

1.00
1.02
1.08
2.30
7.17
1.94
1.01
1.02
1.05
12.43
f1 (ppm)

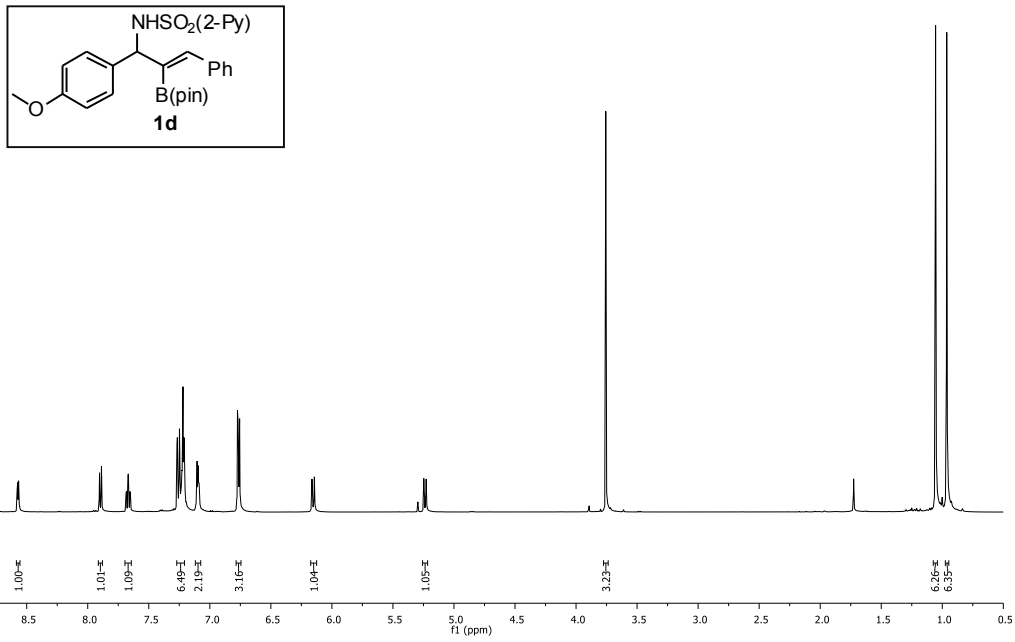

f1 (ppm)
f1 (ppm)

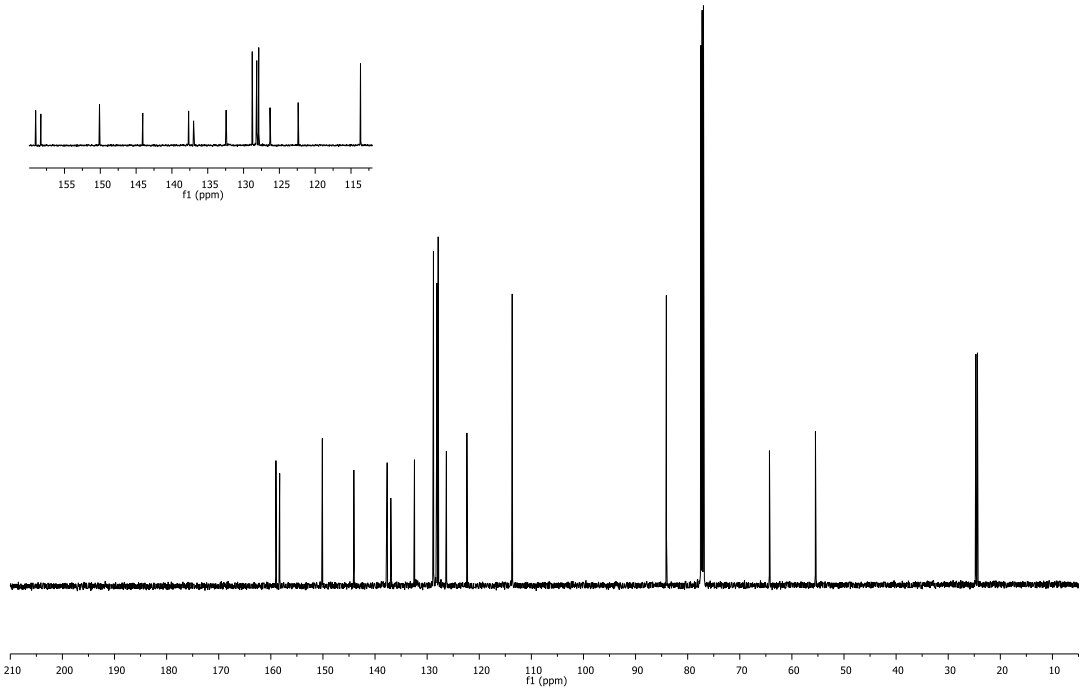

NHSO2(2-Py)
n-Bu
B(pin)
O

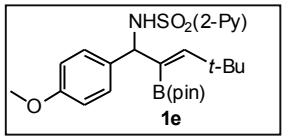
1c


1.00
1.02
1.03
1.12
2.07
2.11
0.99
1.02
1.02
3.16
1.14
1.05
1.55
2.44
12.78
3.21
f1 (ppm)


f1 (ppm)

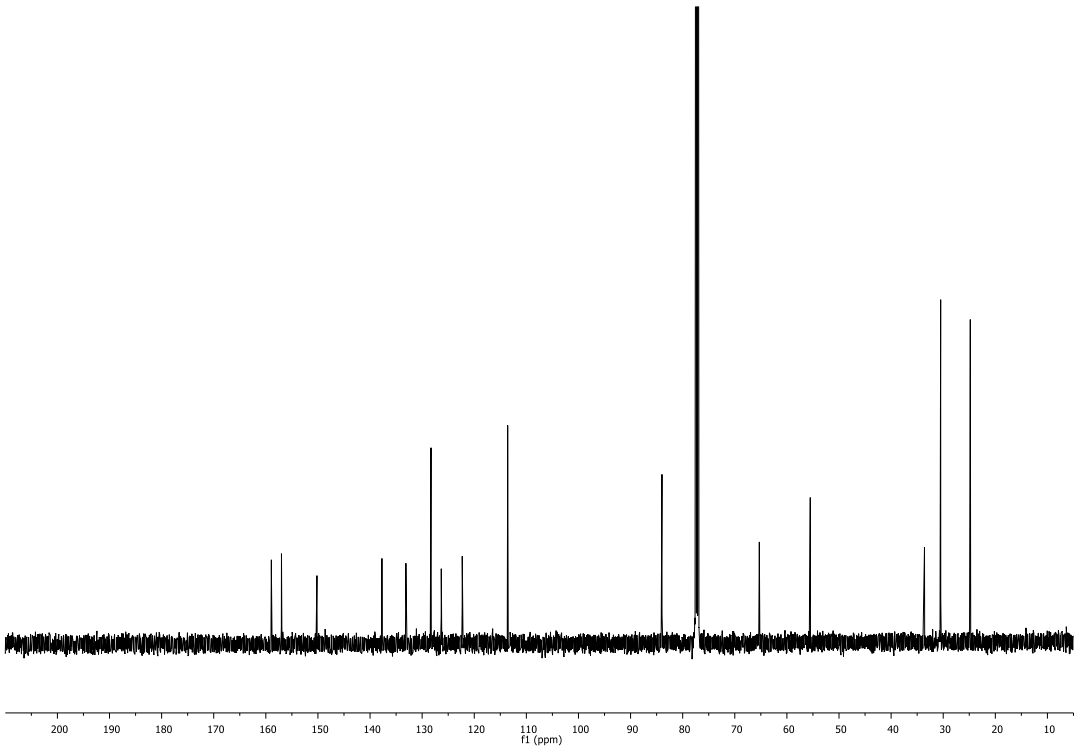

NHSO2(2-Py)
Ph
B(pin)
O
1d
1.00
1.01
1.09
6.49
2.19
3.16
1.04
1.05
3.23
6.26
6.35
f1 (ppm)

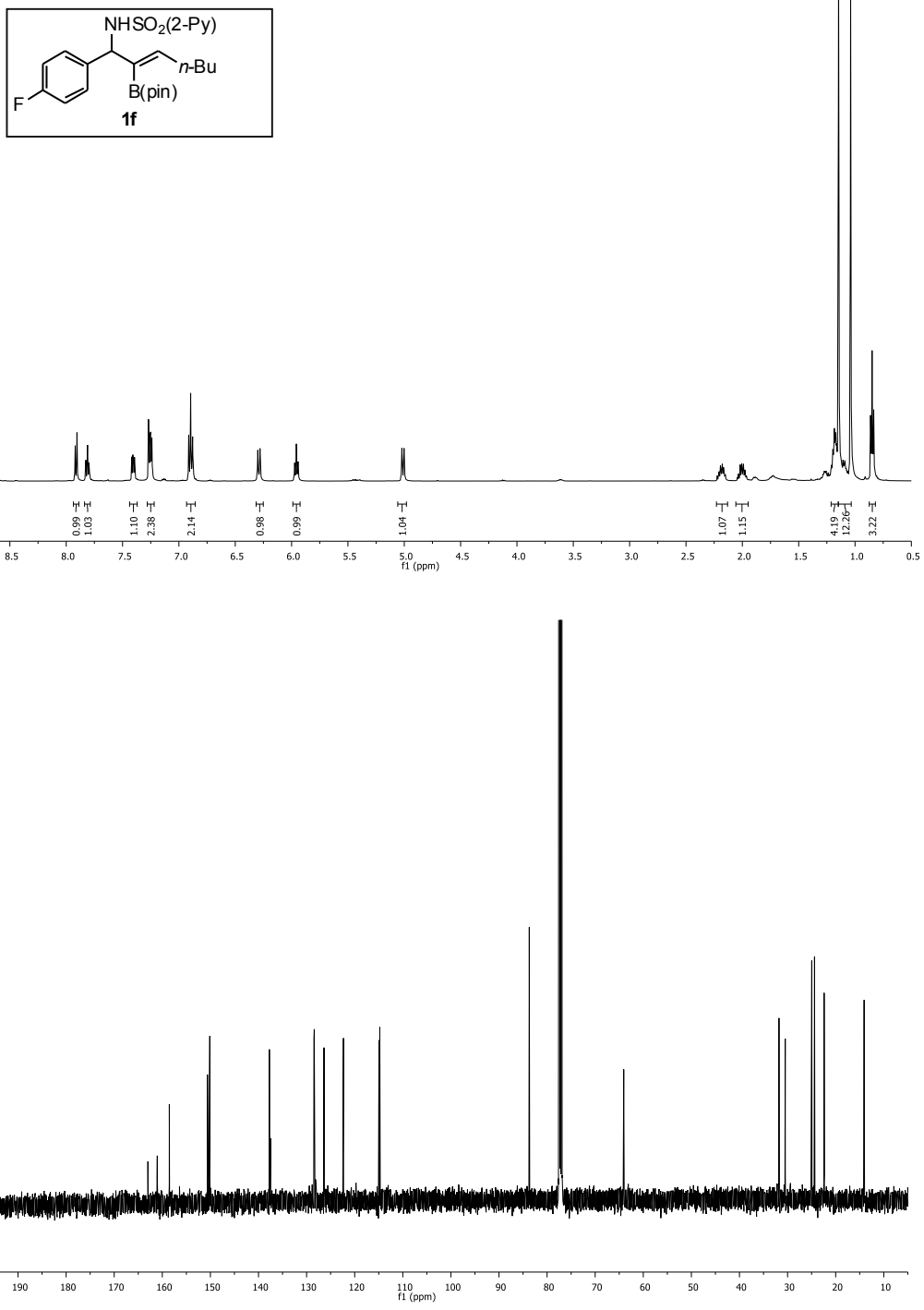

f1 (ppm)
f1 (ppm)

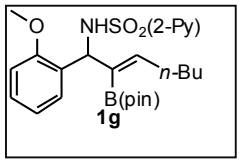

NHSO2(2-Py)
t-Bu
B(pin)
O

1e

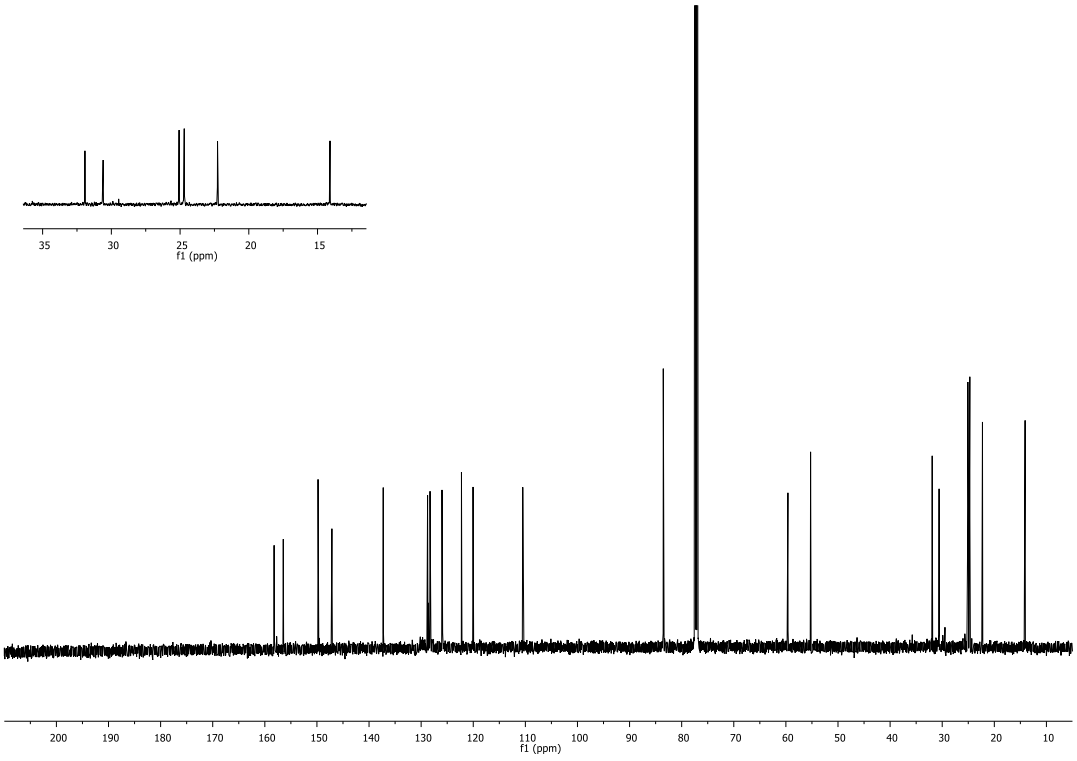
1.00
1.04
0.99
1.03
2.04
2.12
0.97
1.05
1.05
3.18
12.40
9.03
f1 (ppm)

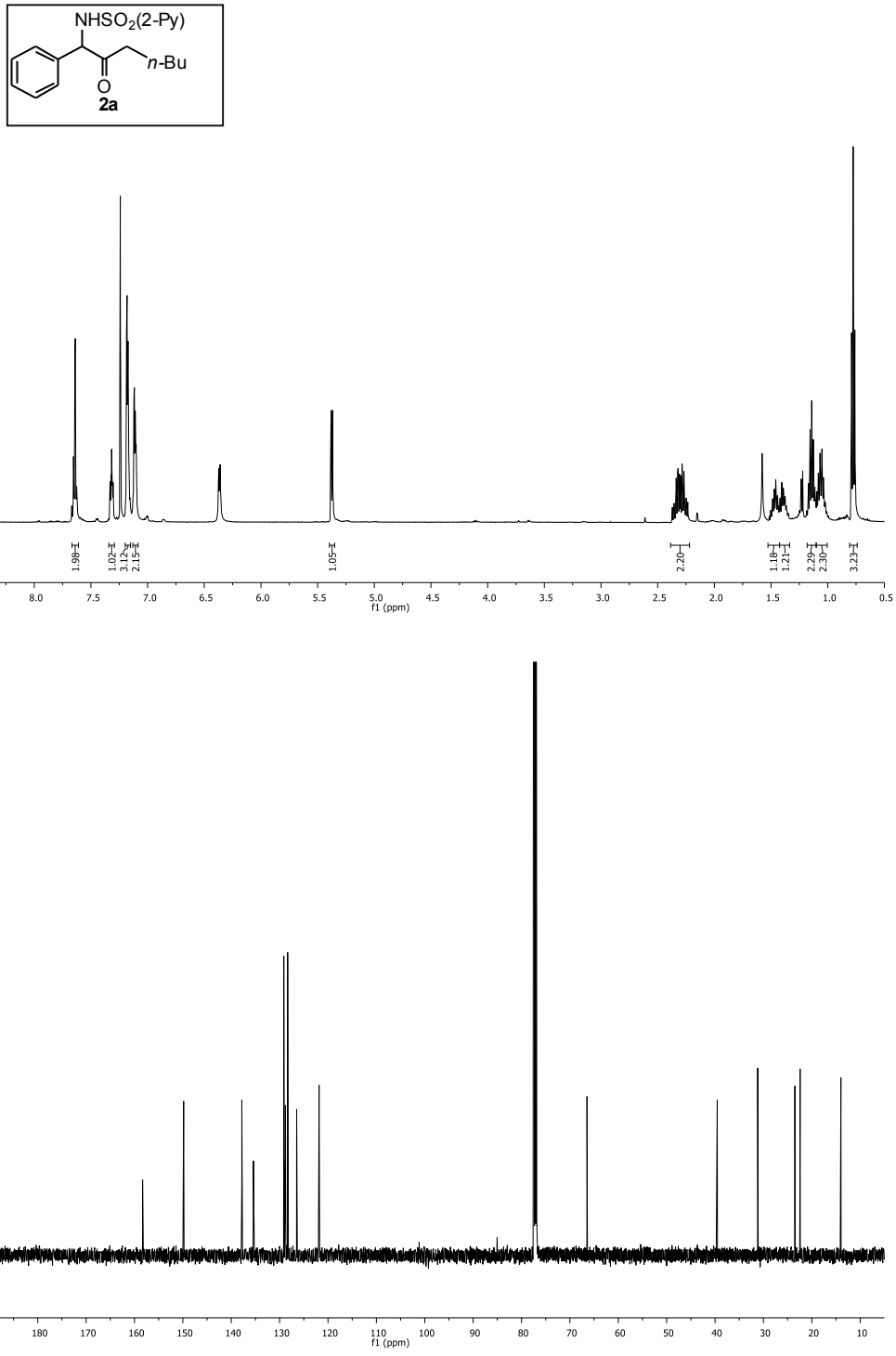

f1 (ppm)

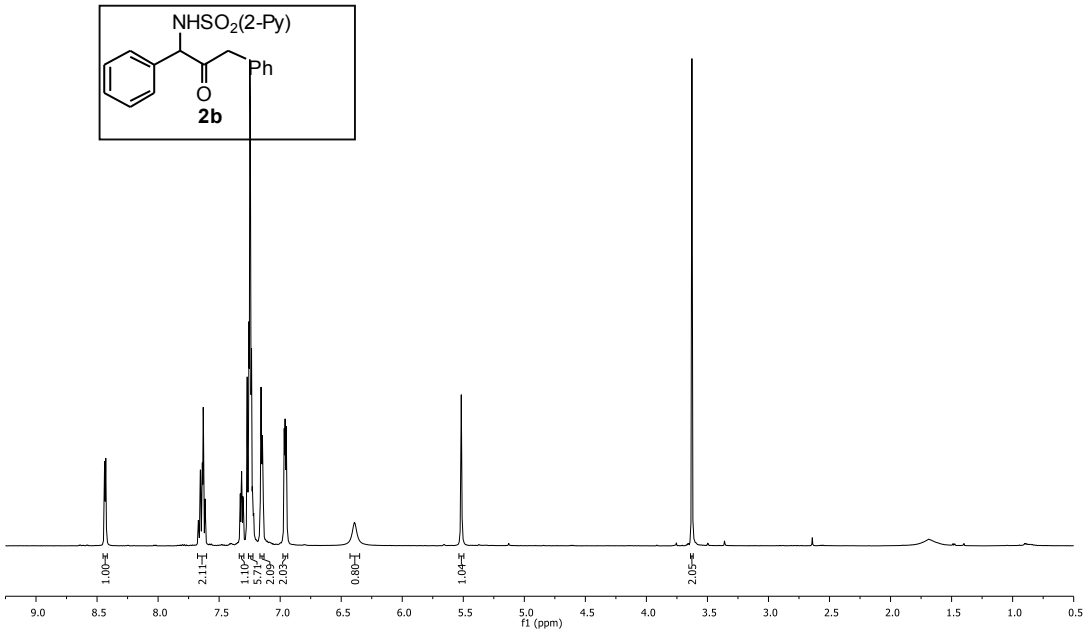

NHSO2(2-Py)
n-Bu
B(pin)
F
1f
0.99
0.99
1.03
1.10
2.38
2.14
0.98
0.99
1.04
1.07
1.15
4.19
12.26
3.22
f1 (ppm)
f1 (ppm)

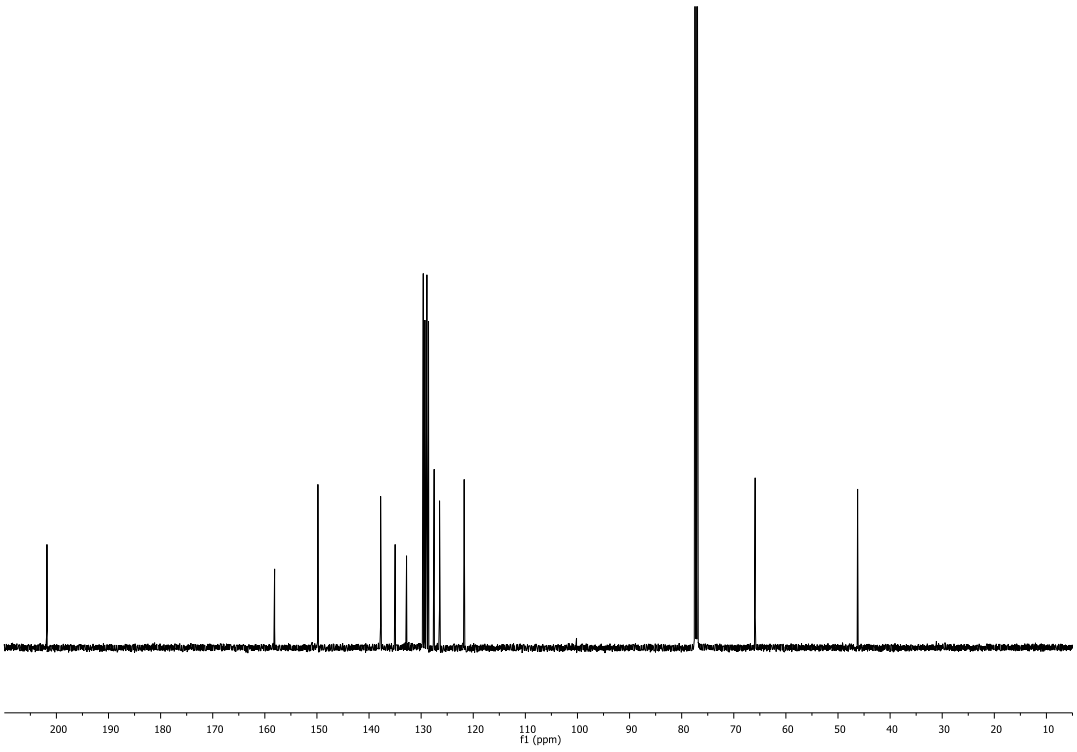

O
NHSO2(2-Py)
n-Bu
B(pin)
1g

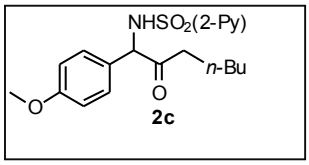
1.00
1.01
1.11
1.11
1.11
1.08
1.09
1.06
1.02
1.05
1.04
3.12
2.19
16.23
3.32
f1 (ppm)


f1 (ppm)
f1 (ppm)

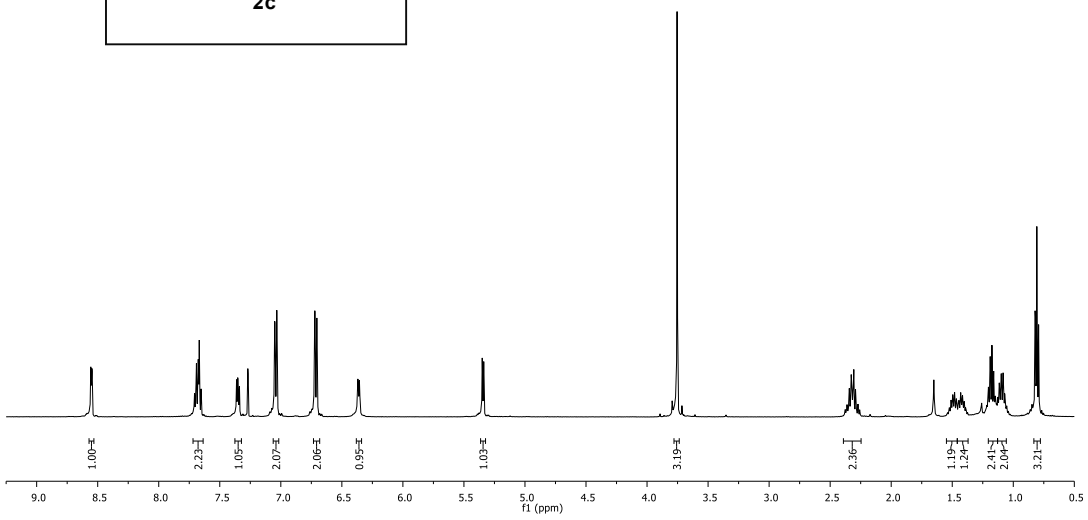

NHSO2(2-Py)
n-Bu
O
2a
1.00
1.98
1.02
3.12
2.15
1.05
2.20
1.18
1.21
2.29
2.30
3.23
f1 (ppm)
f1 (ppm)

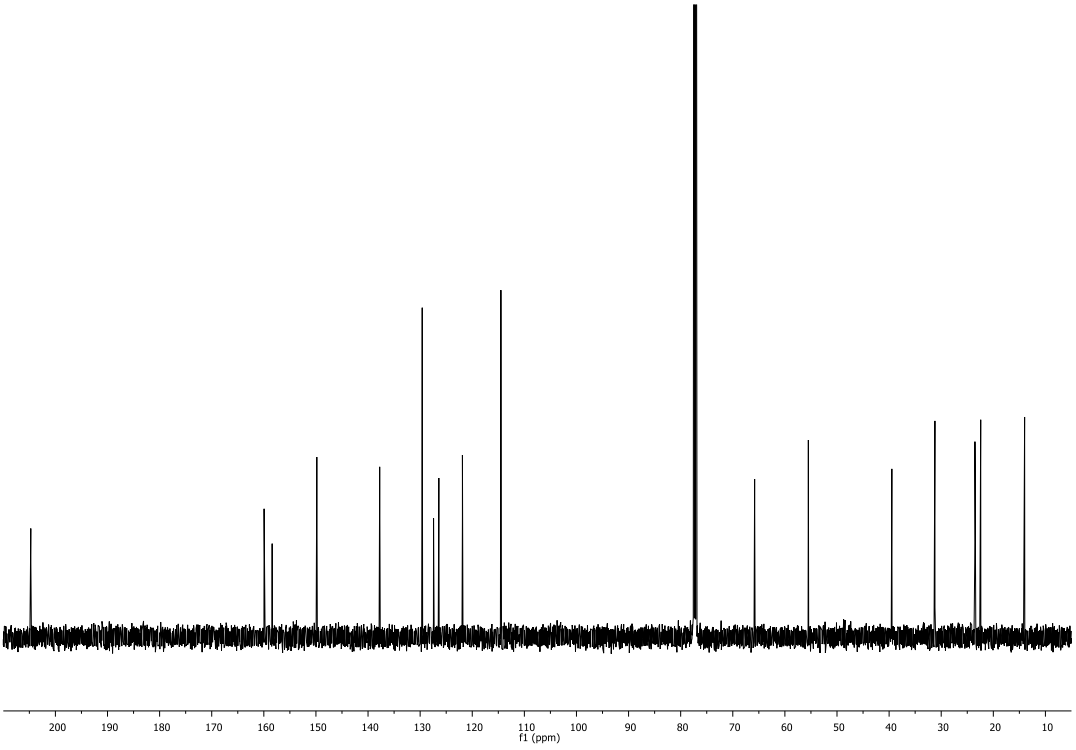

NHSO2(2-Py)
Ph
O
2b
1.00
2.11
1.10
5.71
2.09
2.03
0.80
1.04
2.05
f1 (ppm)

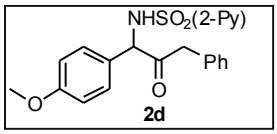

f1 (ppm)

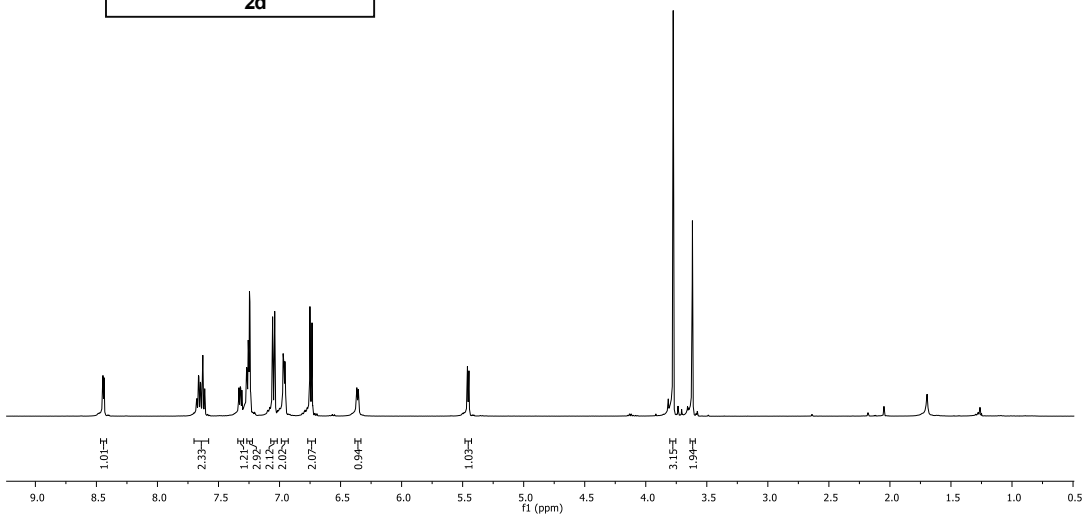

NHSO2(2-Py)
n-Bu
O
O

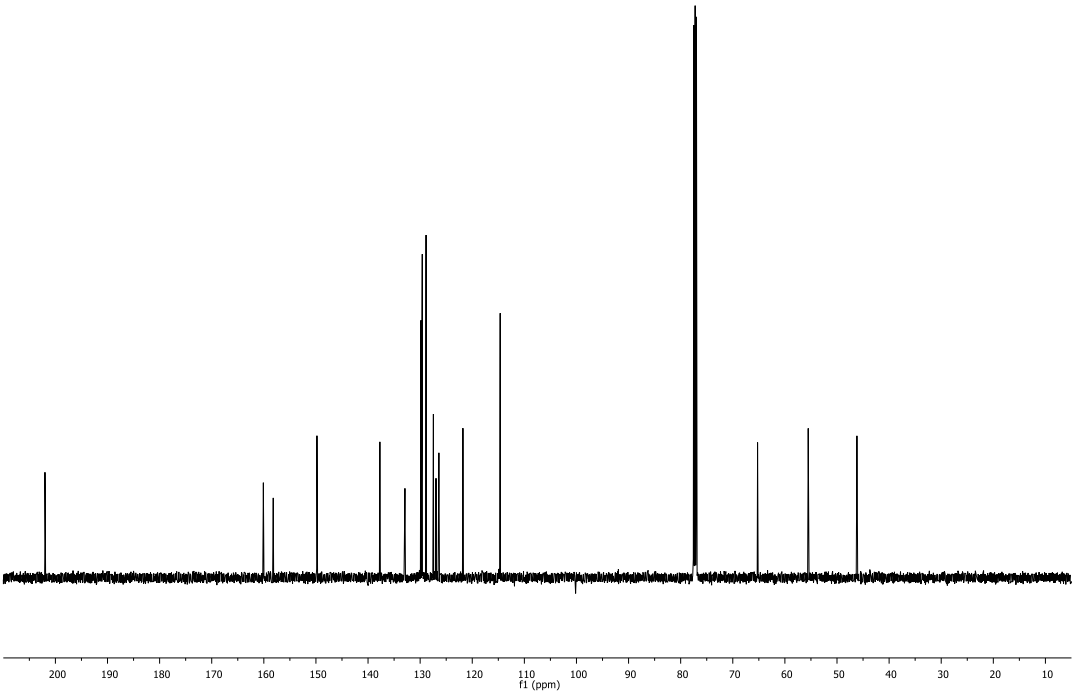
2c

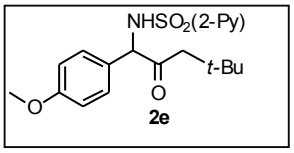

1.00
2.23
1.05
2.07
2.06
0.95
1.03
3.19
2.36
1.19
1.24
2.41
2.04
3.21
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

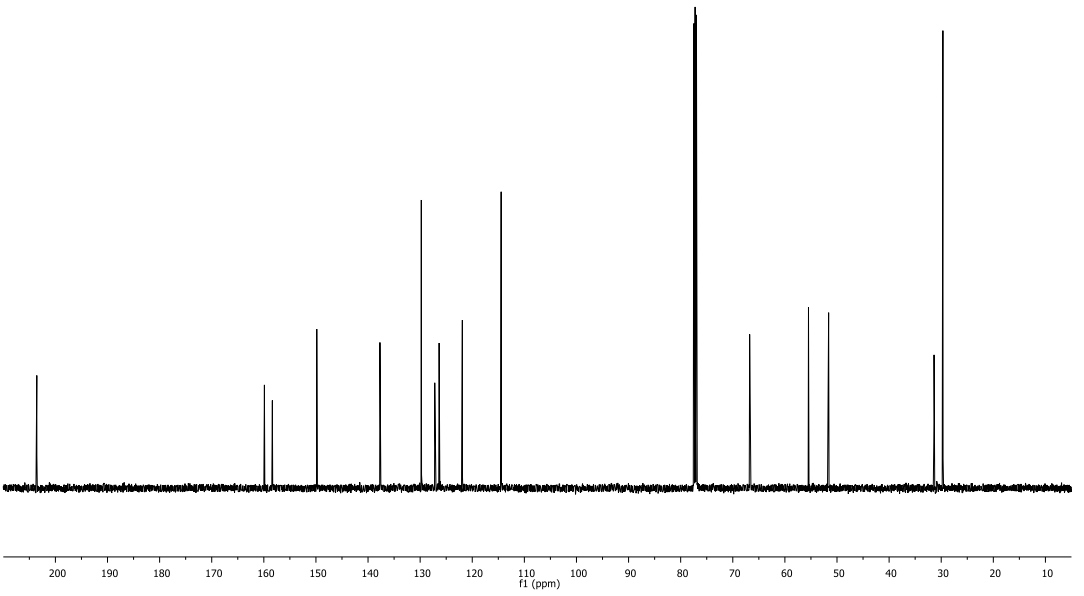

NHSO2(2-Py)
Ph
O
O
2d

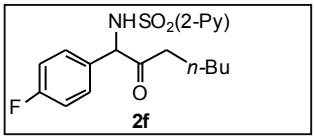

1.01
2.33
1.21
2.92
2.12
2.02
2.07
0.94
1.03
3.15
1.94
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

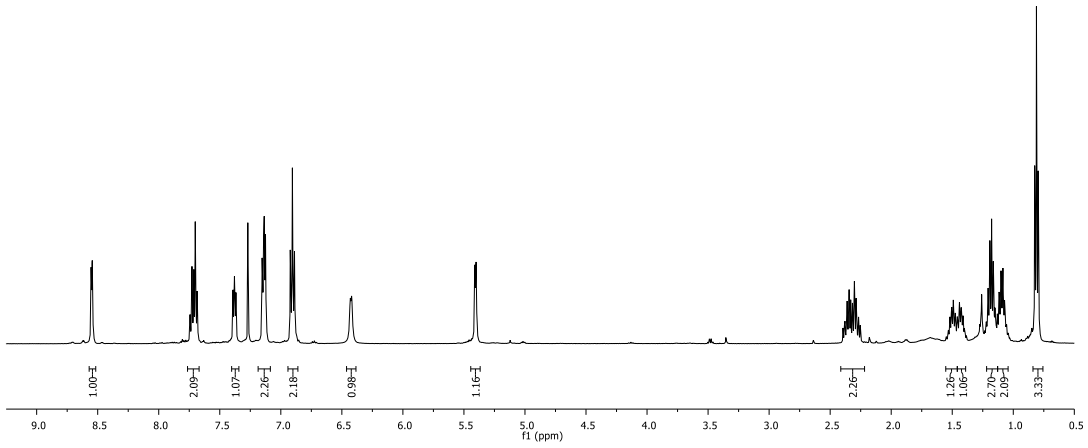

NHSO2(2-Py)
t-Bu
O
O
2e

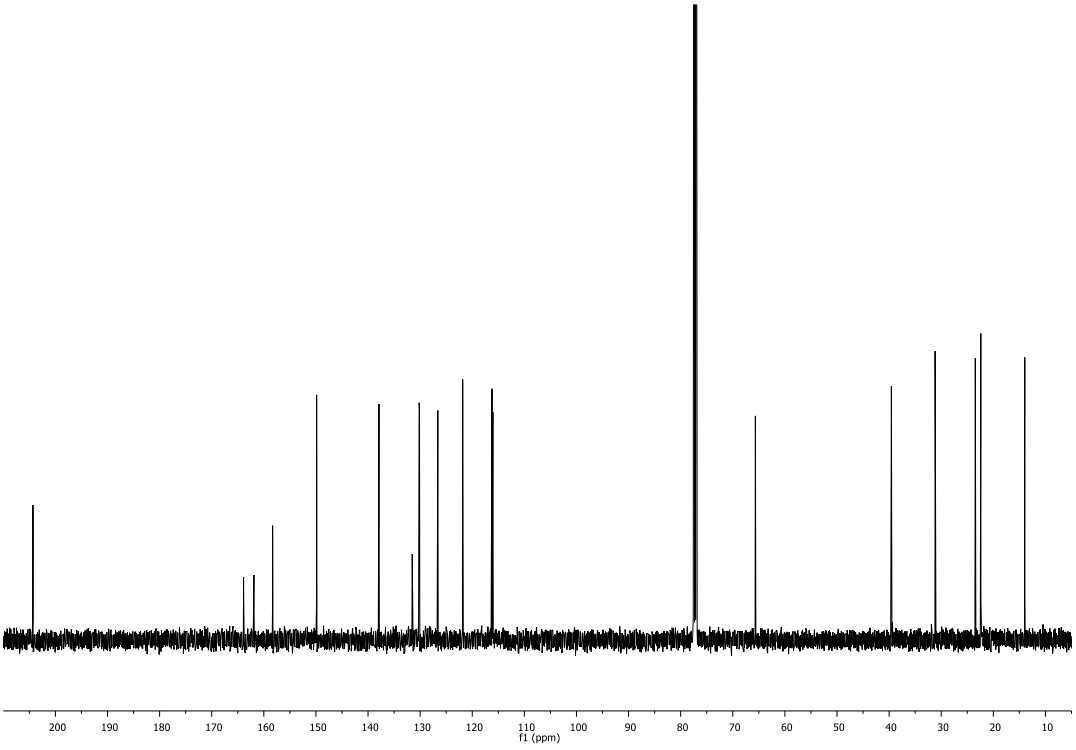
1.00
2.08
1.04
2.10
2.07
0.93
1.03
3.00
1.04
1.08
9.14
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

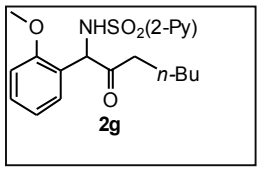

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


NHSO2(2-Py)
n-Bu
O
F

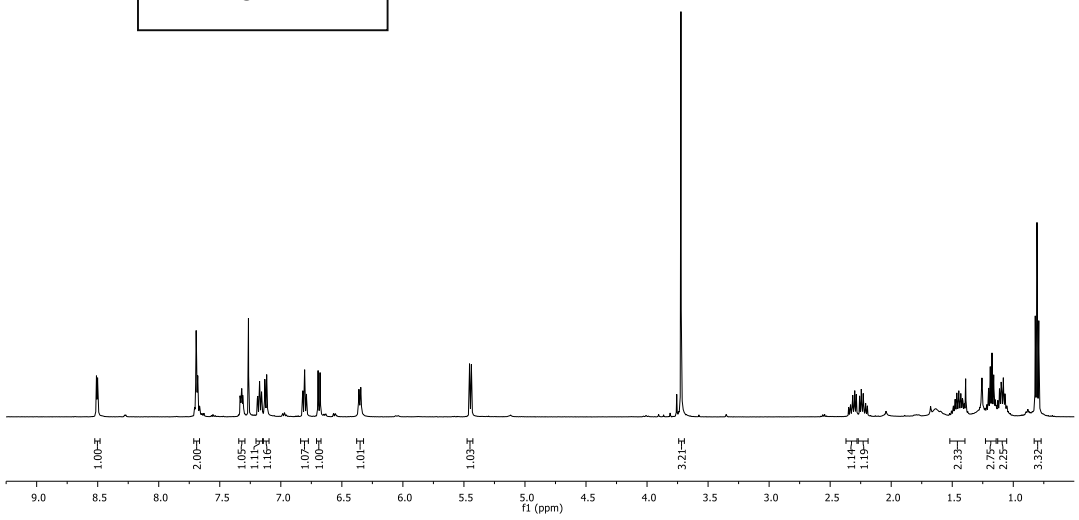
2f

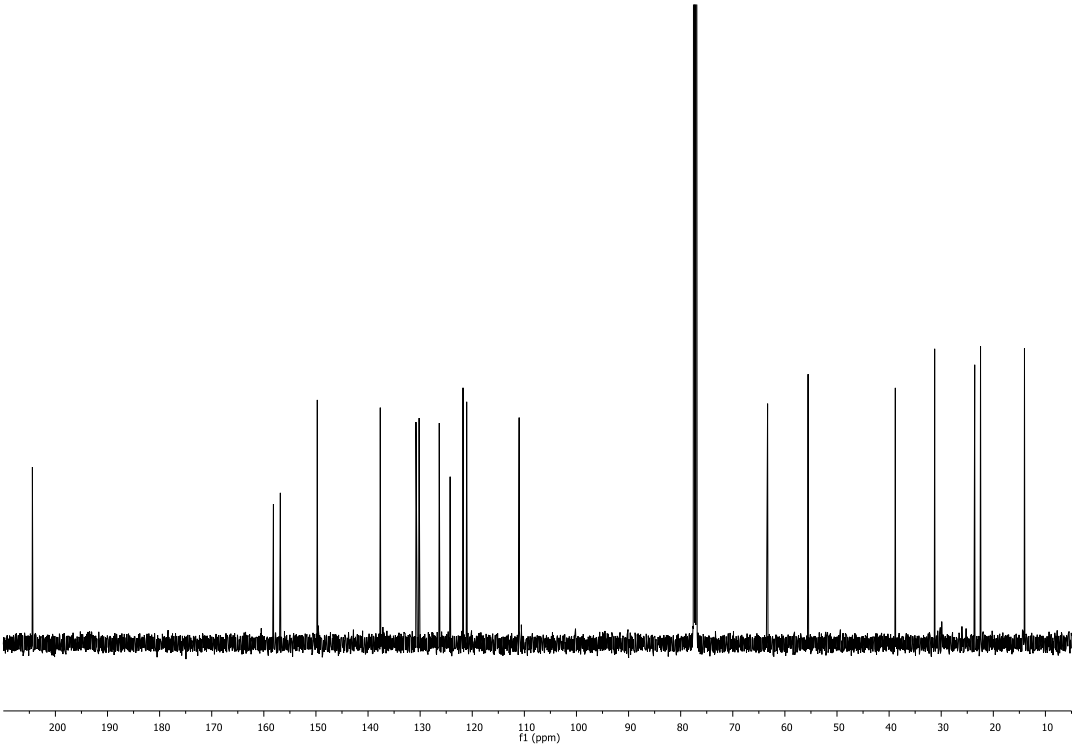

1.00
2.09
1.07
2.26
2.18
0.98
1.16
2.26
1.26
1.06
2.70
2.09
3.33
f1 (ppm)

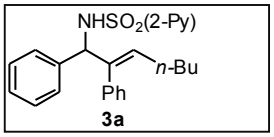

f1 (ppm)


O
NHSO2(2-Py)
n-Bu
O

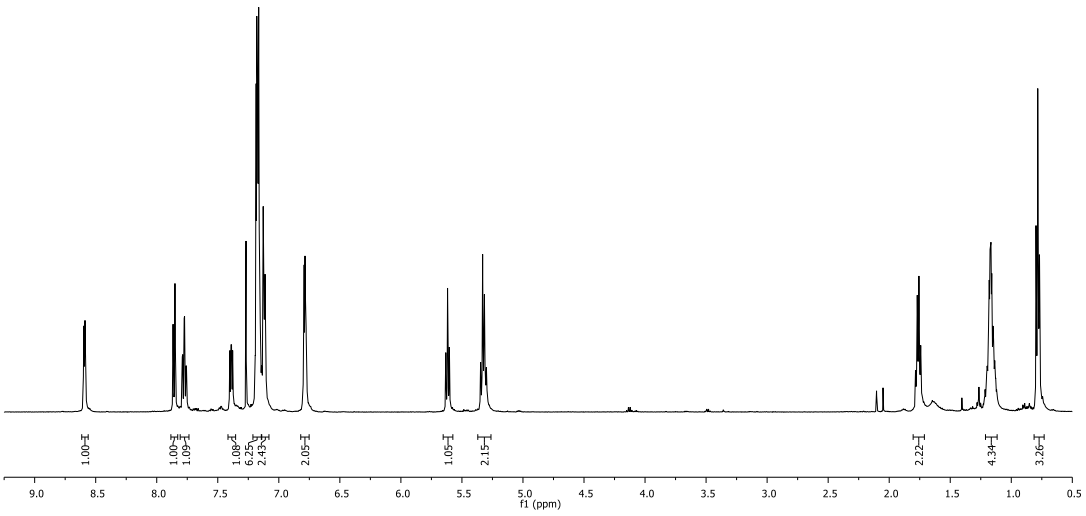
2g

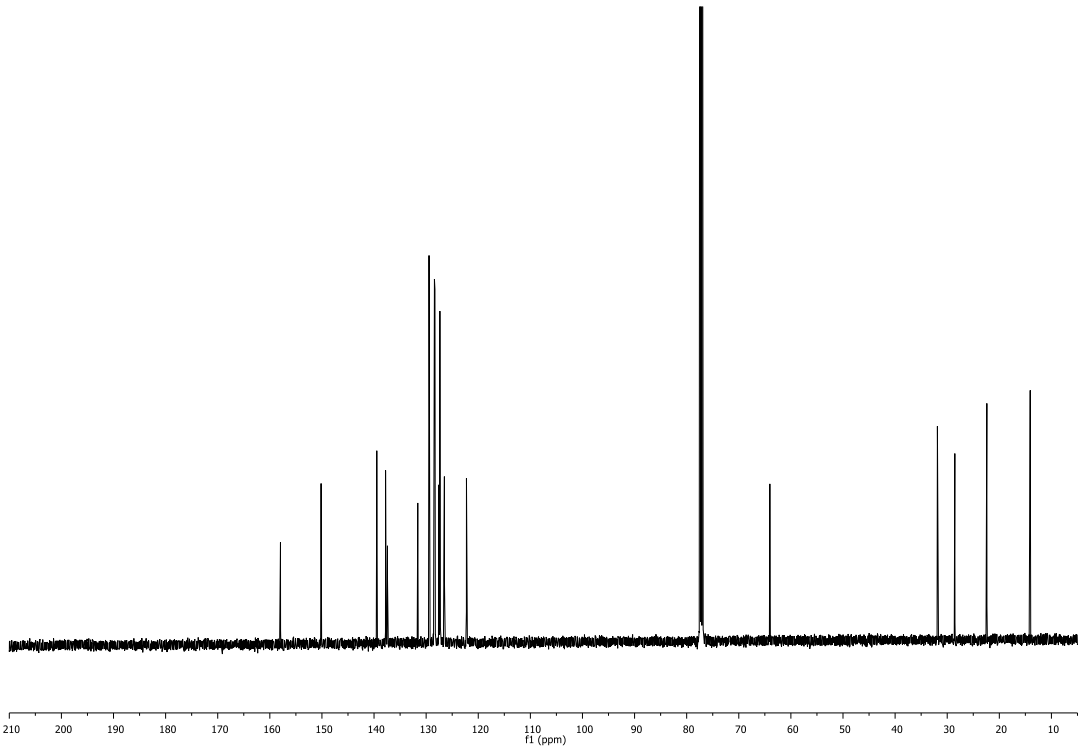

1.00
2.00
1.05
1.11
1.16
1.07
1.00
1.01
1.03
3.21
1.14
1.19
2.33
2.75
2.25
3.32
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

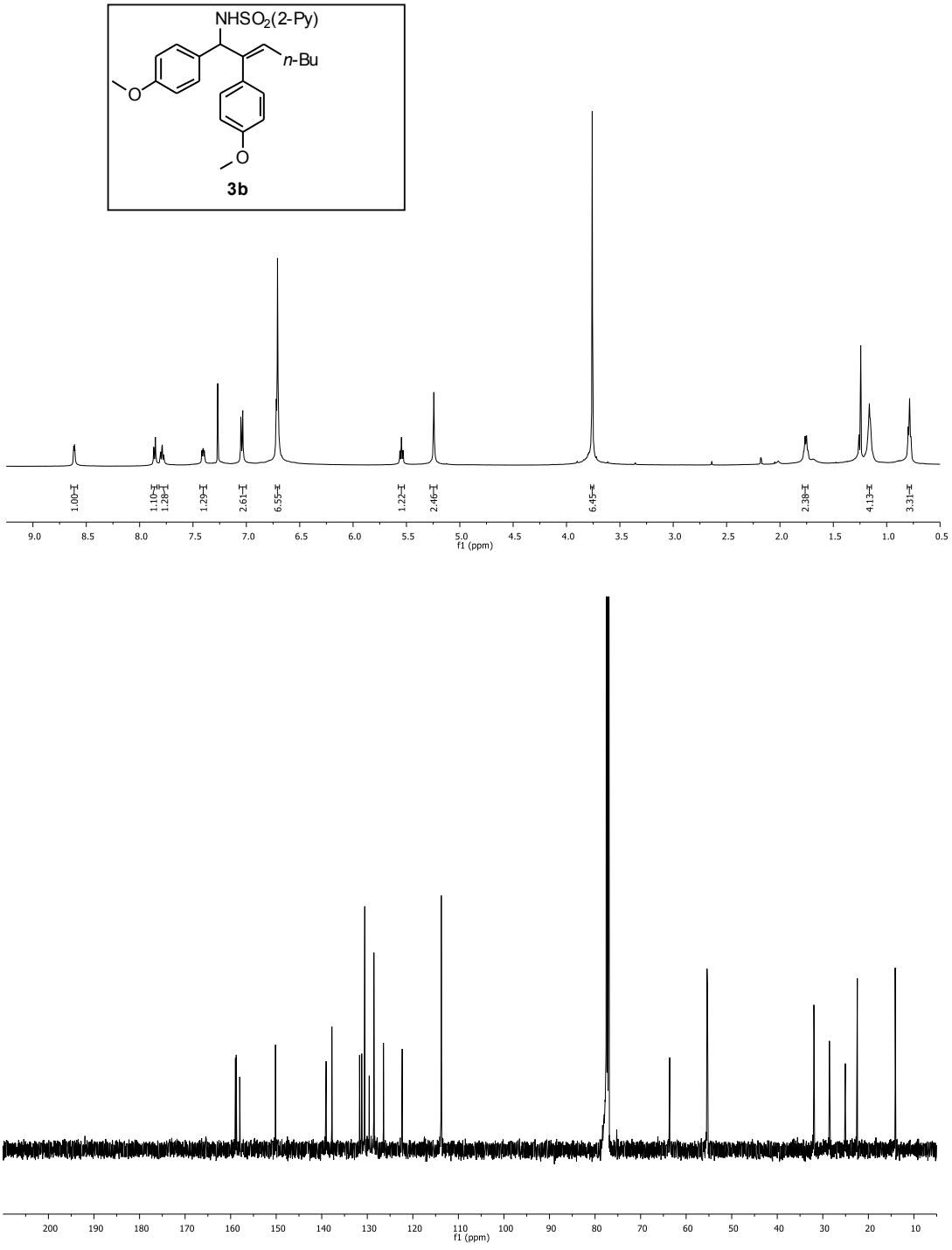

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

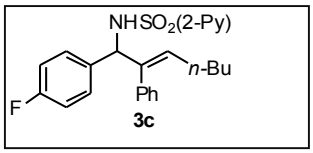

NHSO2(2-Py)
n-Bu
Ph

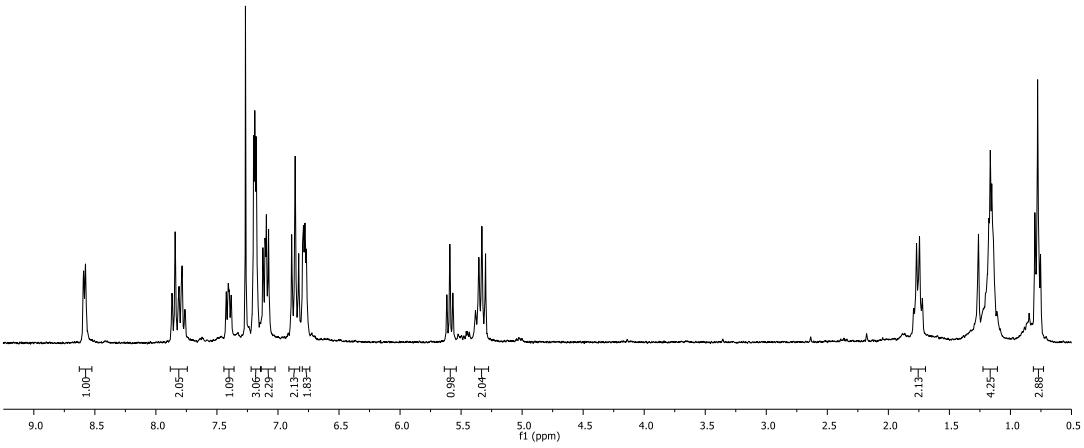
3a

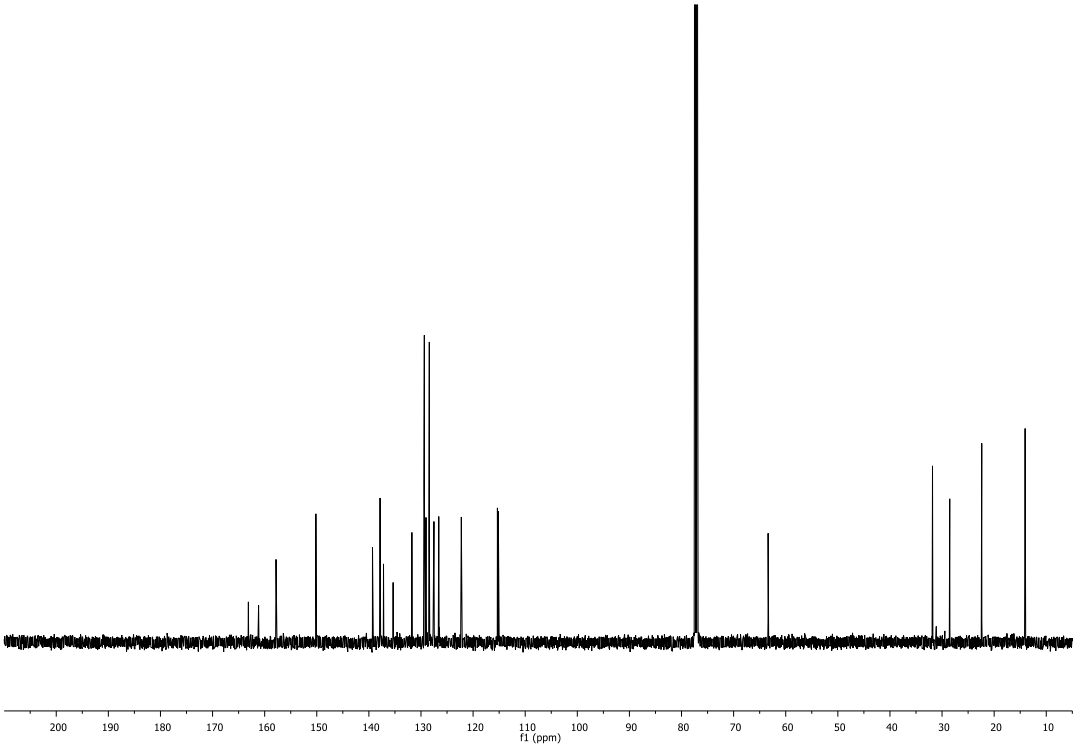

1.00
1.00
1.09
1.08
6.25
2.43
2.05
1.05
2.15
2.22
4.34
3.26
f1 (ppm)

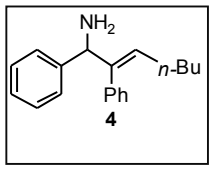

f1 (ppm)


NHSO2(2-Py)
n-Bu
O
O
3b
1.00
1.10
1.28
1.29
2.61
6.55
1.22
2.46
6.45
2.38
4.13
3.31
f1 (ppm)
f1 (ppm)

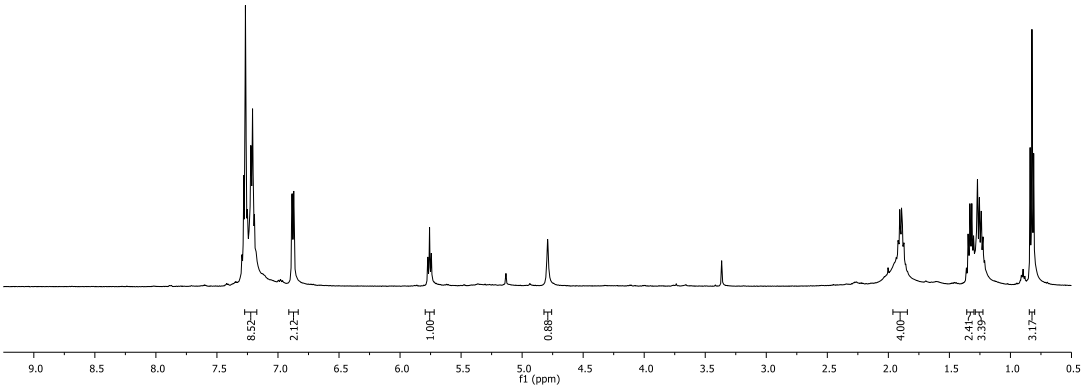

NHSO2(2-Py)
n-Bu
Ph
F
3c

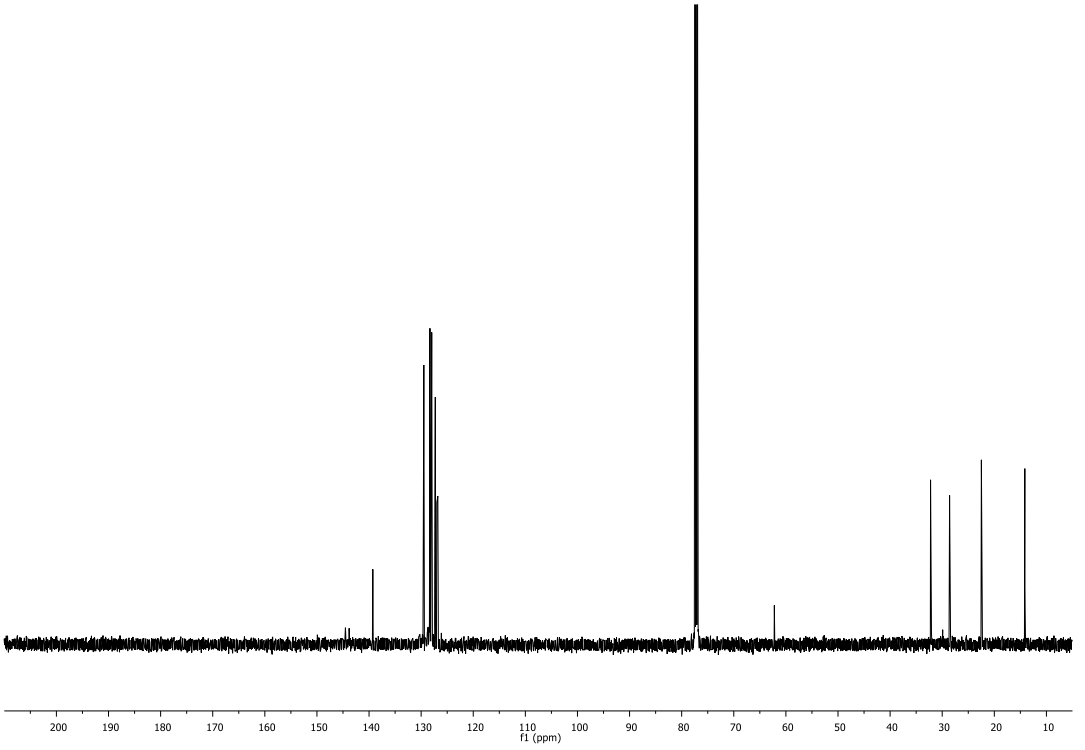

1.00
2.05
1.09
3.06
2.29
2.13
1.83
0.98
2.04
2.13
4.25
2.88
f1 (ppm)

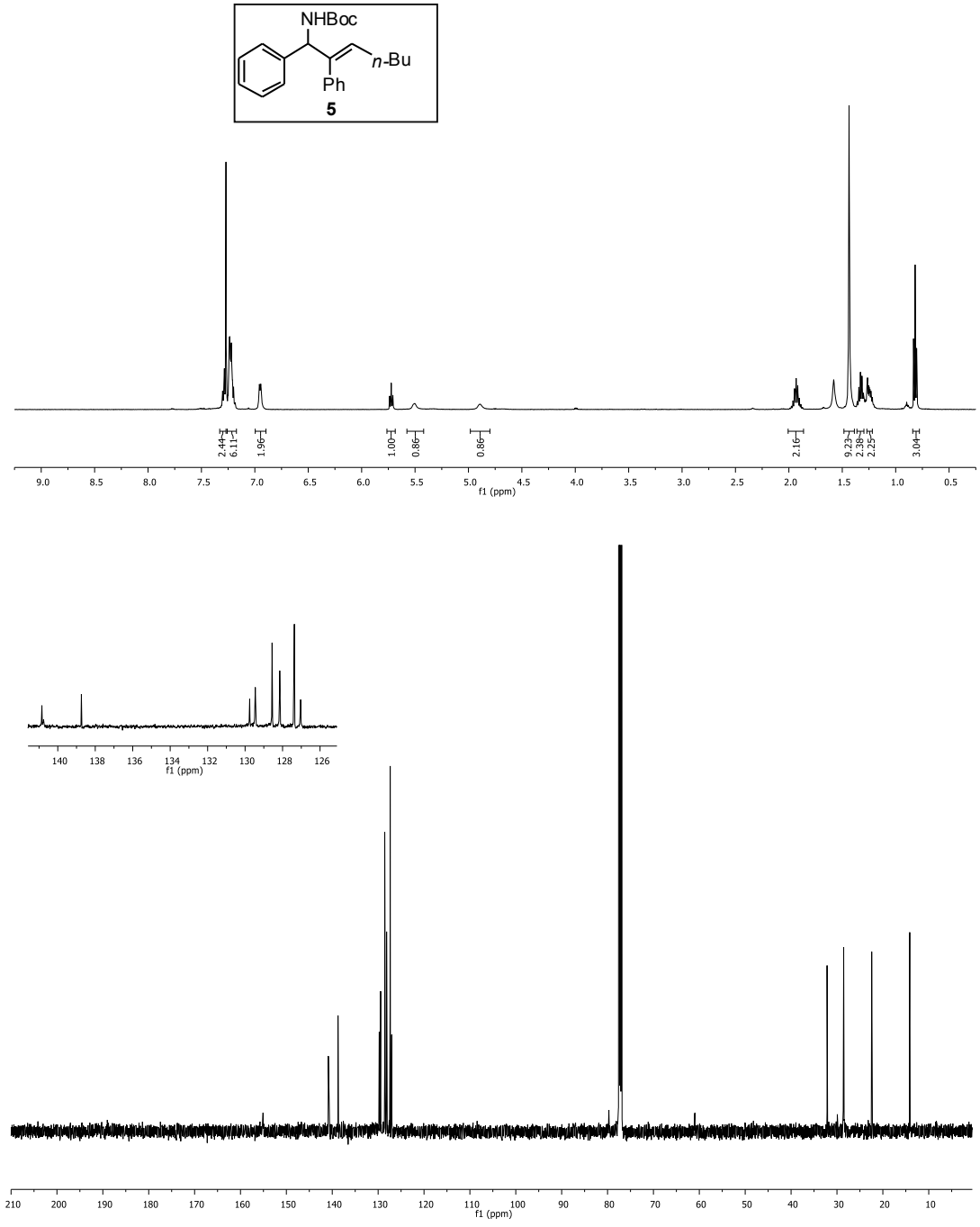

f1 (ppm)


NH2
n-Bu
Ph

4


8.52
2.12
1.00
0.88
4.00
2.41
3.39
3.17
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


NHBoc
n-Bu
Ph
5
2.44
6.11
1.96
1.00
0.86
0.86
2.16
9.23
2.38
2.29
3.04
f1 (ppm)

Appendix A1 NMR Spectra Relavant to Chapter 4

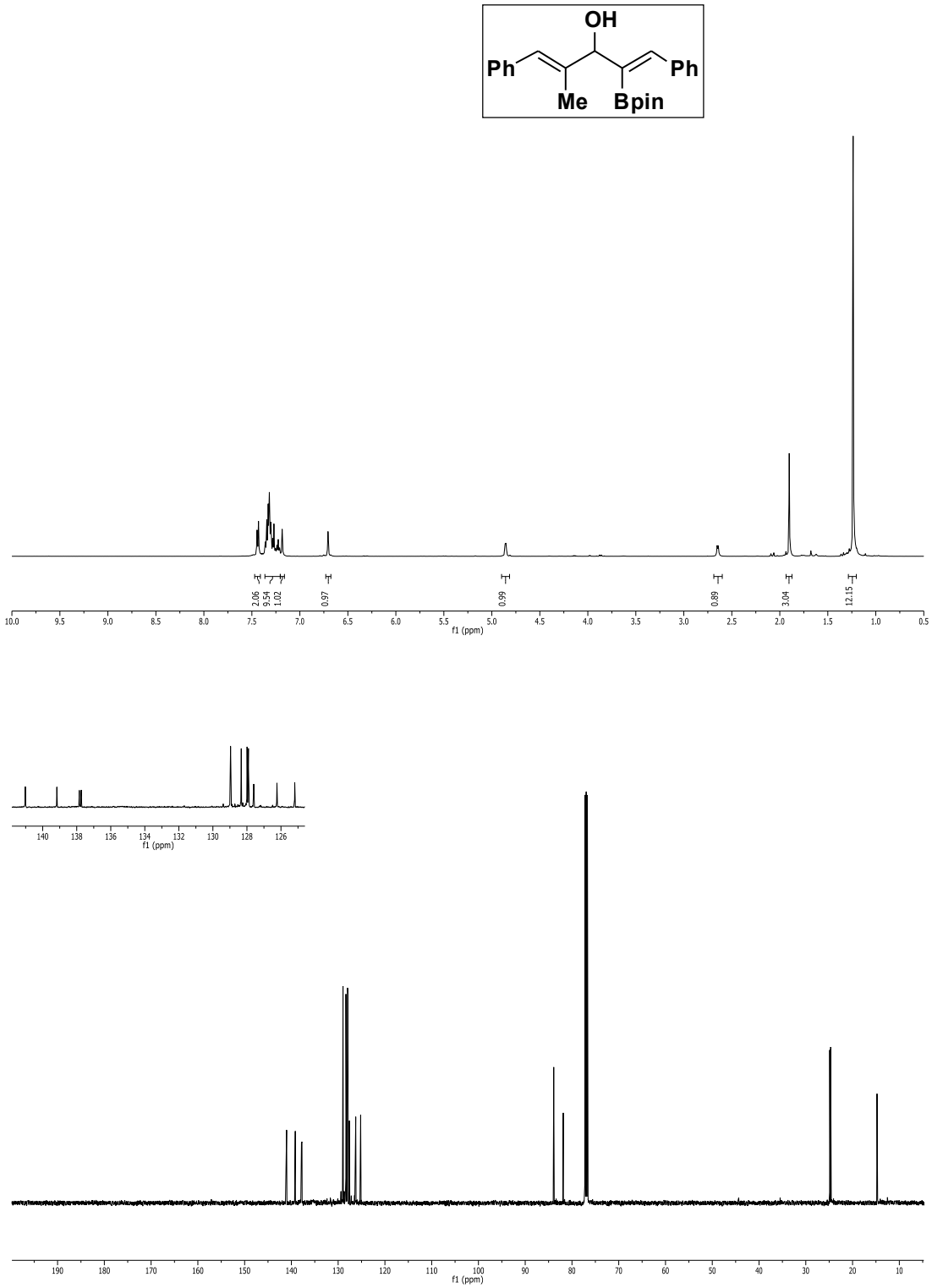


Figure S1 **(1k).** 300 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of (1*E*,4*E*)-2-methyl-1,5-diphenyl-4(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)penta-1,4-dien-3-ol in $CDCl_3$.

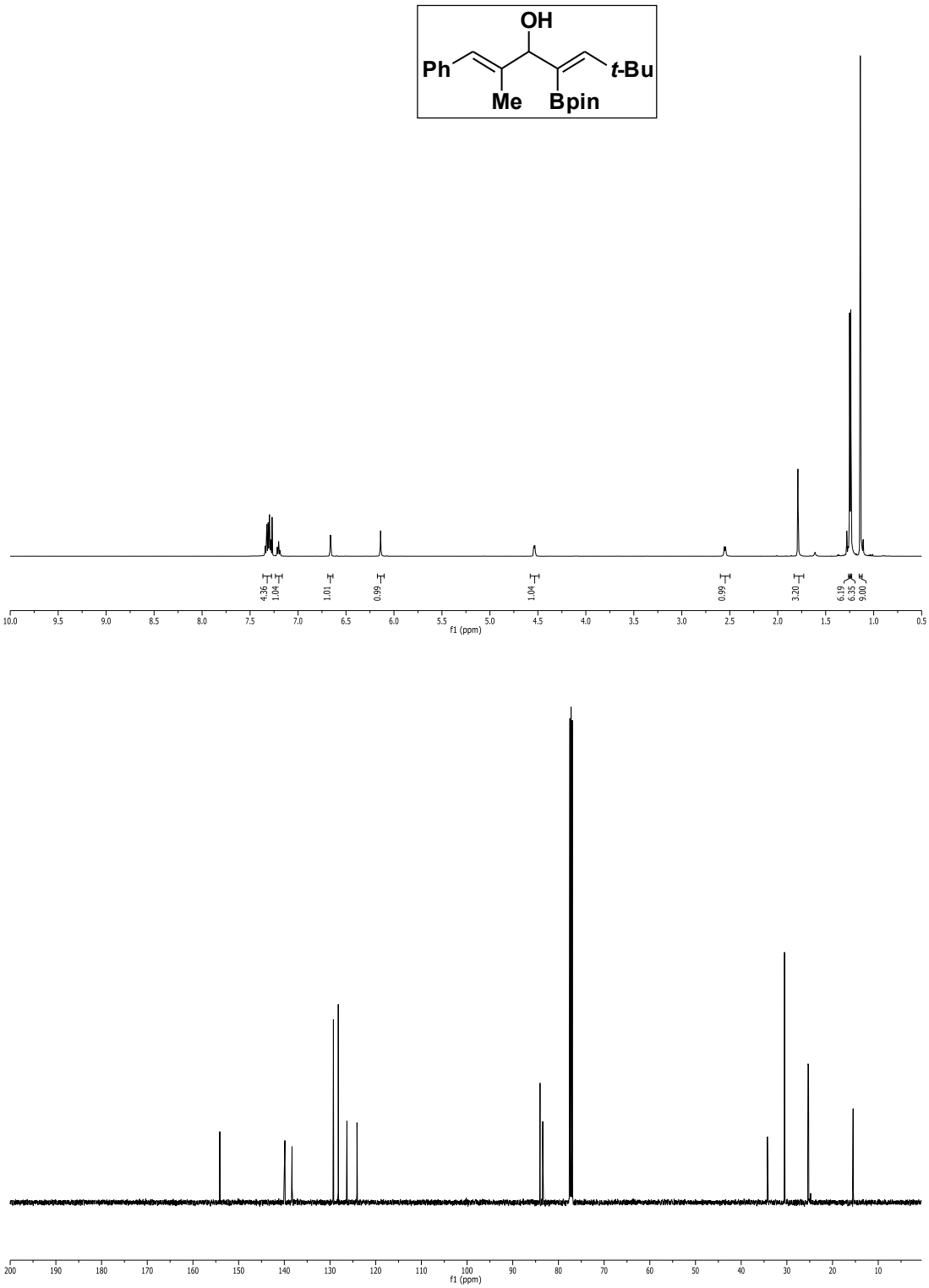


Figure S2 **(1l).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of (1*E*,4*E*)-2,6,6-trimethyl-1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-1,4-dien-3-ol in $CDCl_3$.

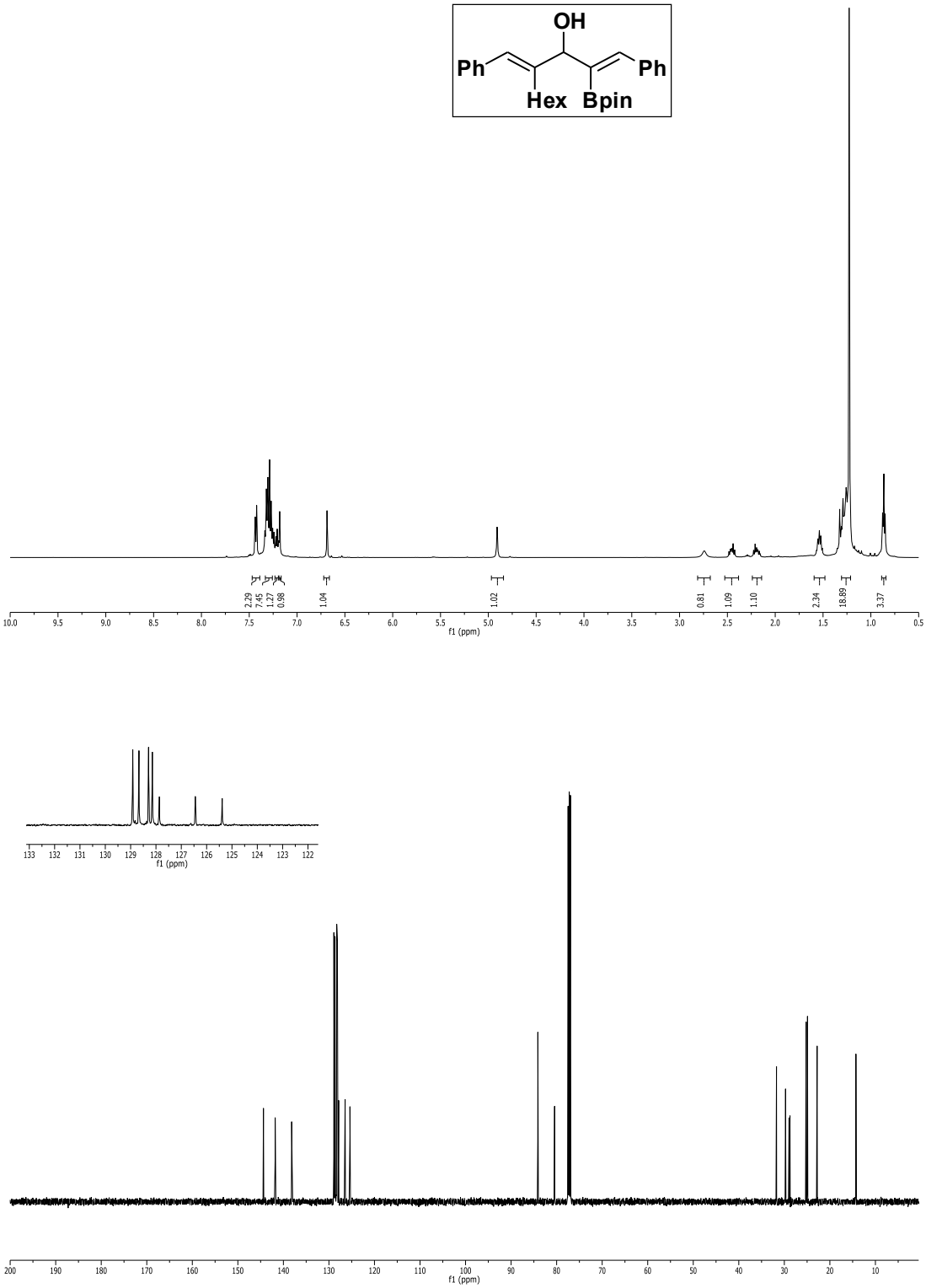


Figure S3 **(1m).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of (1*E*,4*E*)-4-benzylidene-1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dec-1-en-3-ol in $CDCl_3$.

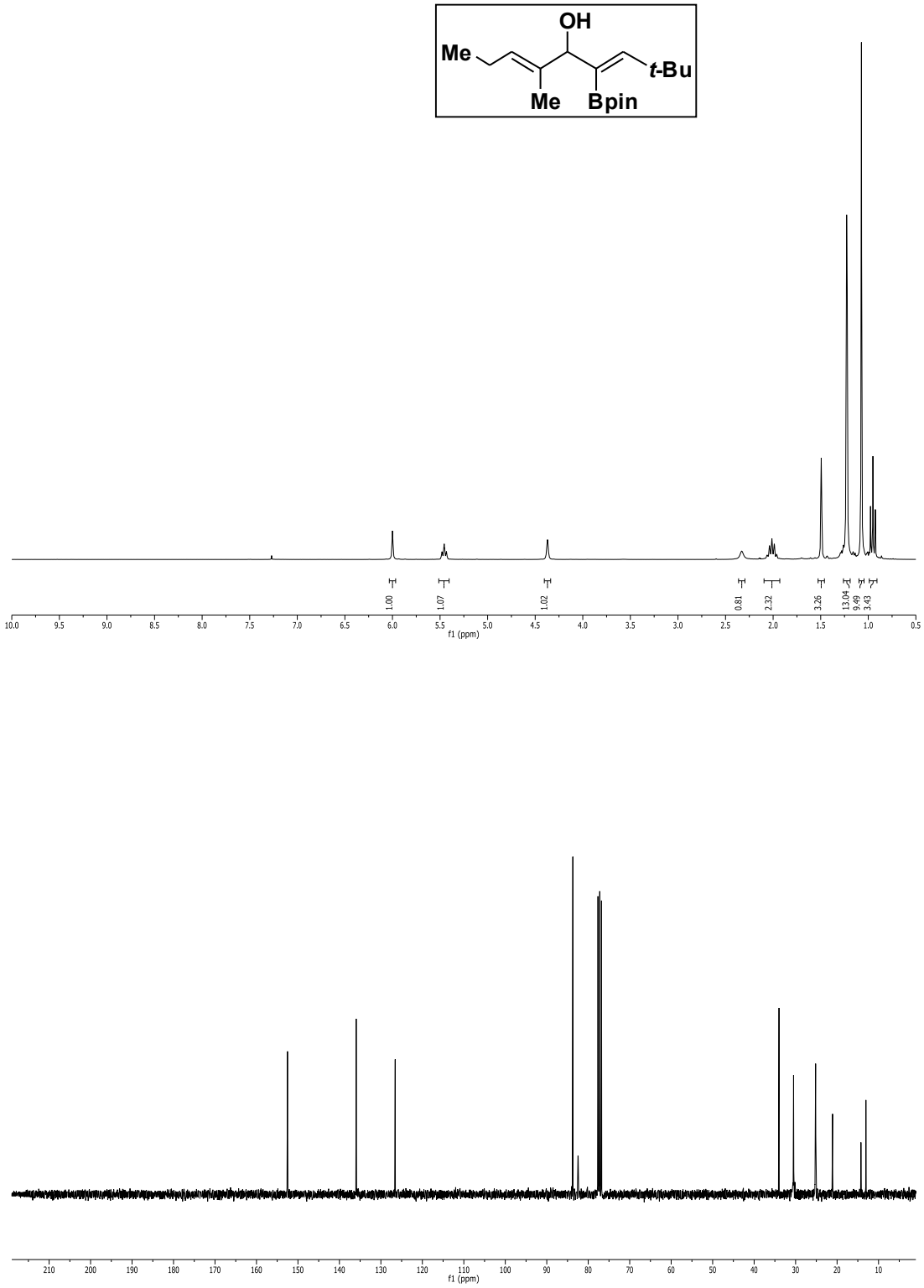


Figure S4 **(1n).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of (3*E*,6*E*)-2,2,6-trimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nona-3,6-dien-5-ol in $CDCl_3$.

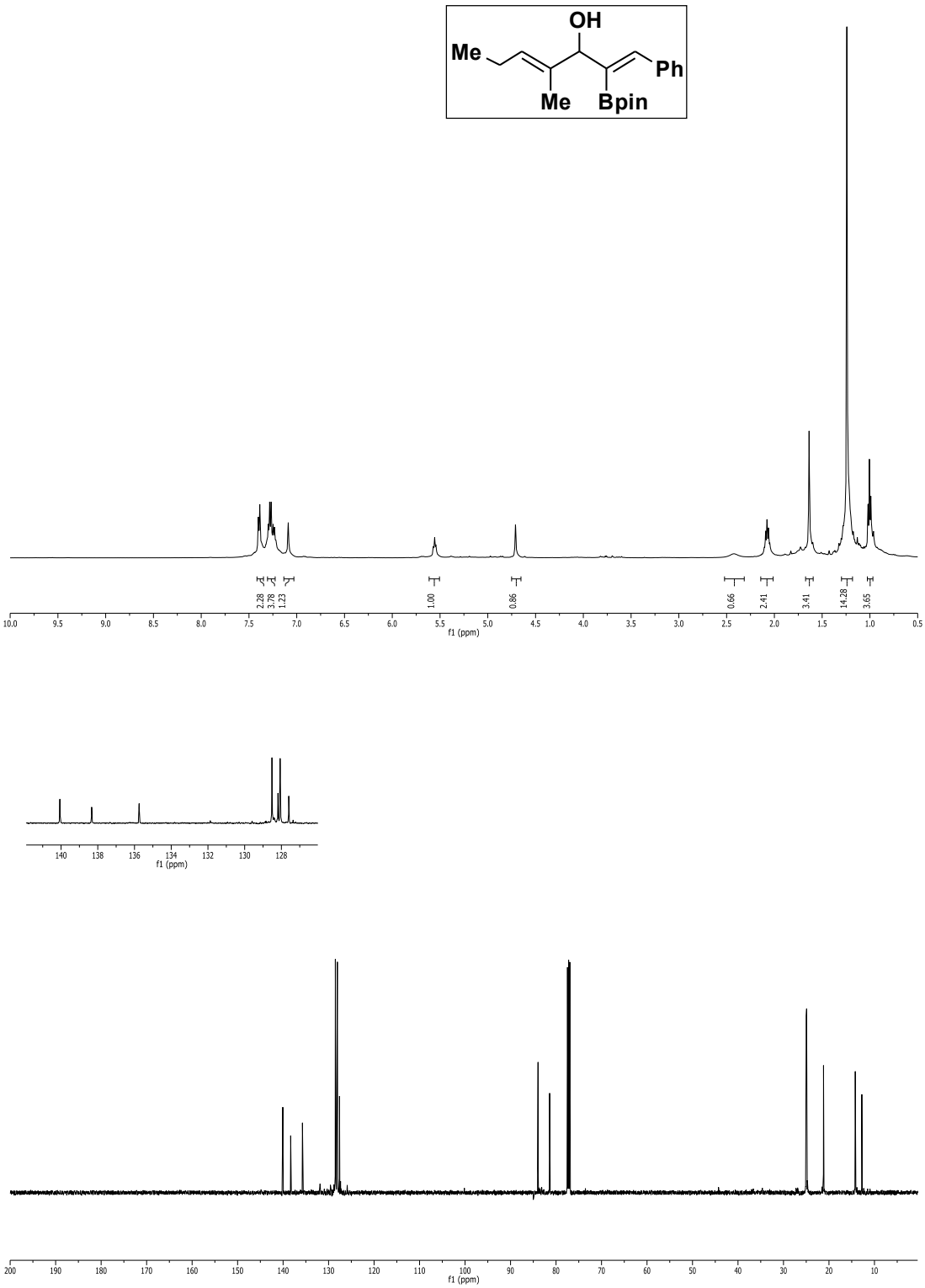


Figure S5 **(1o).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of (1*E*,4*E*)-4-methyl-1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-1,4-dien-3-ol in $CDCl_3$.

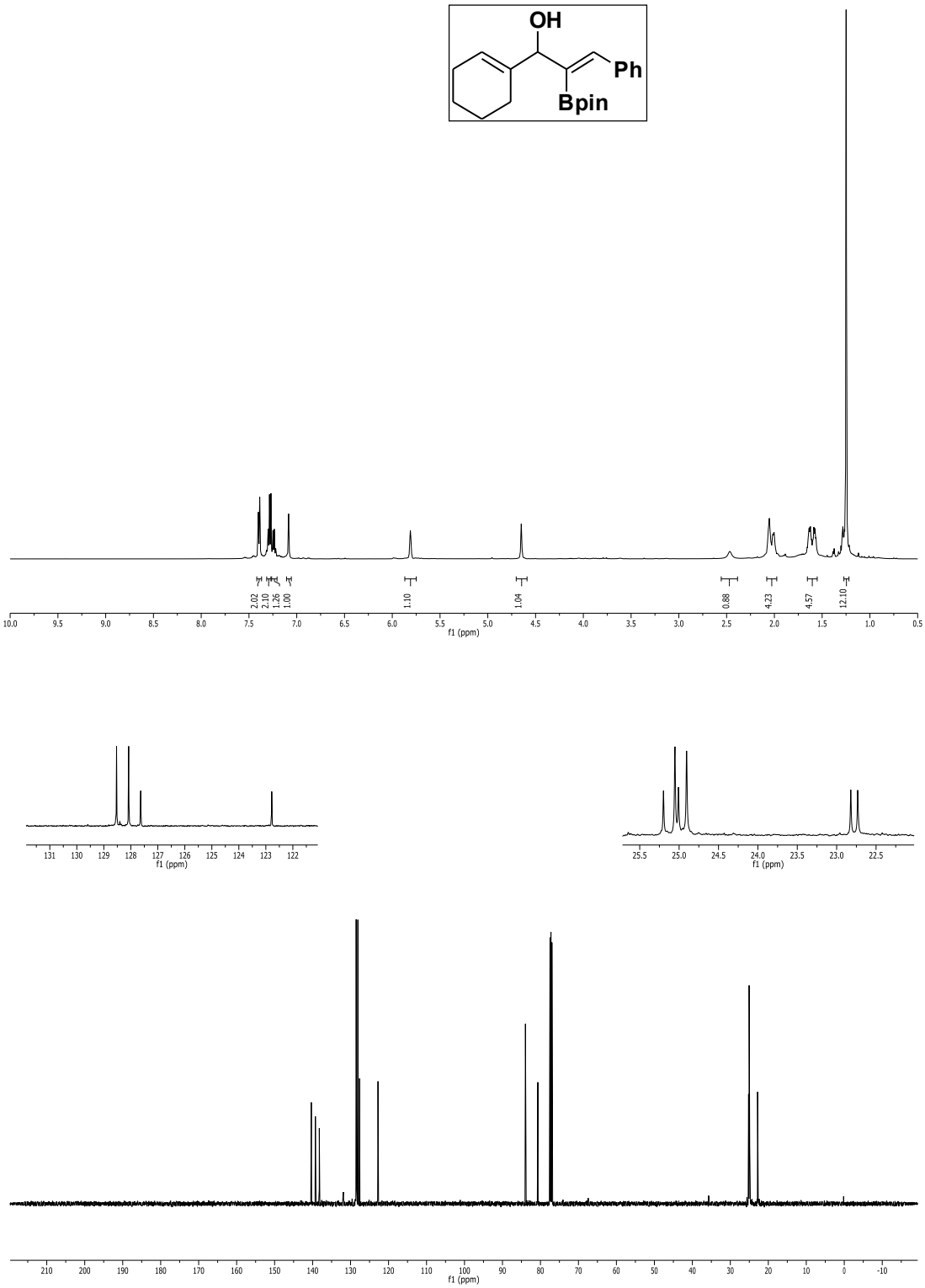


Figure S6 **(1p).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **(***E***)**-1-cyclohexenyl-3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-en-1-ol in $CDCl_3$.

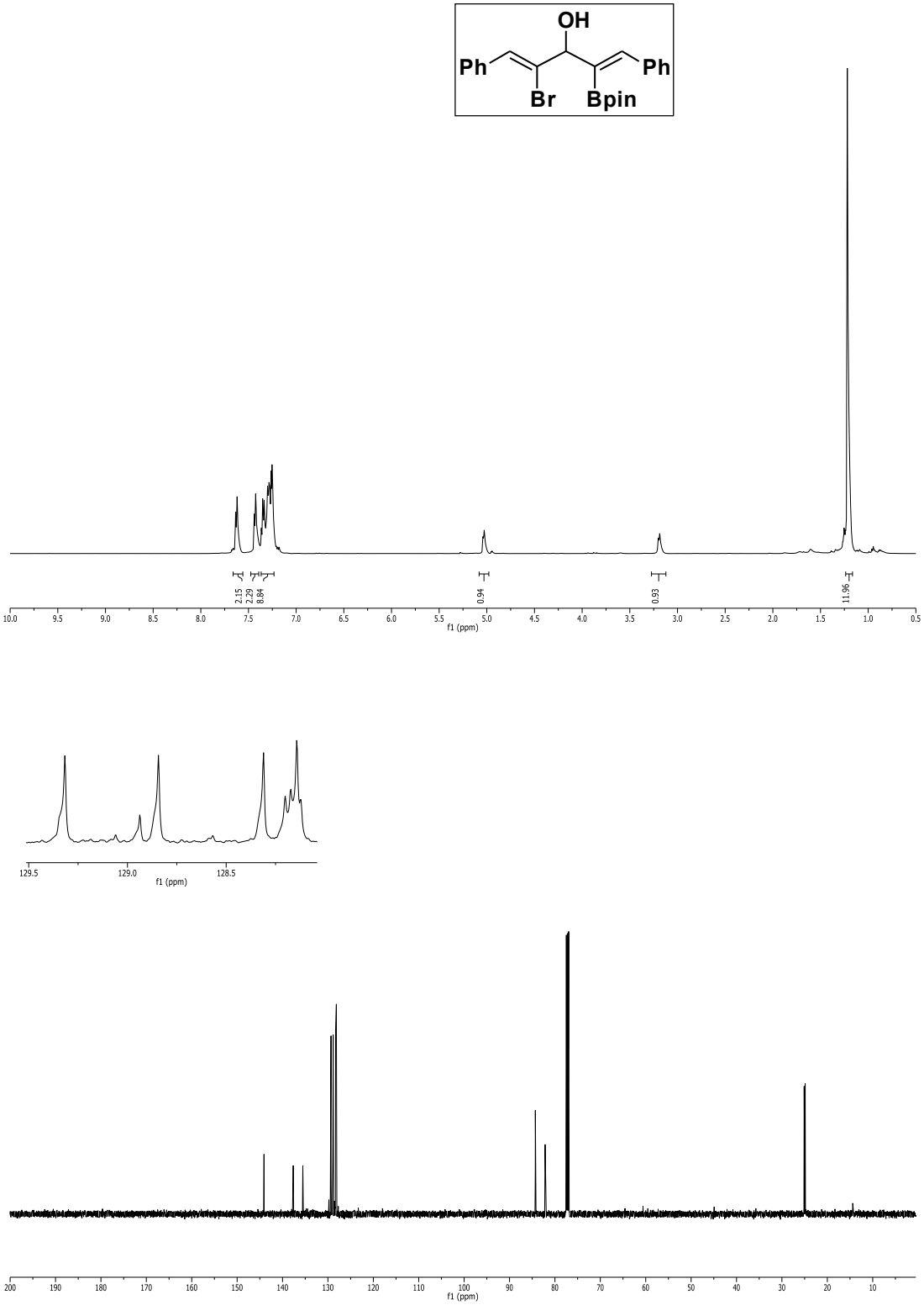
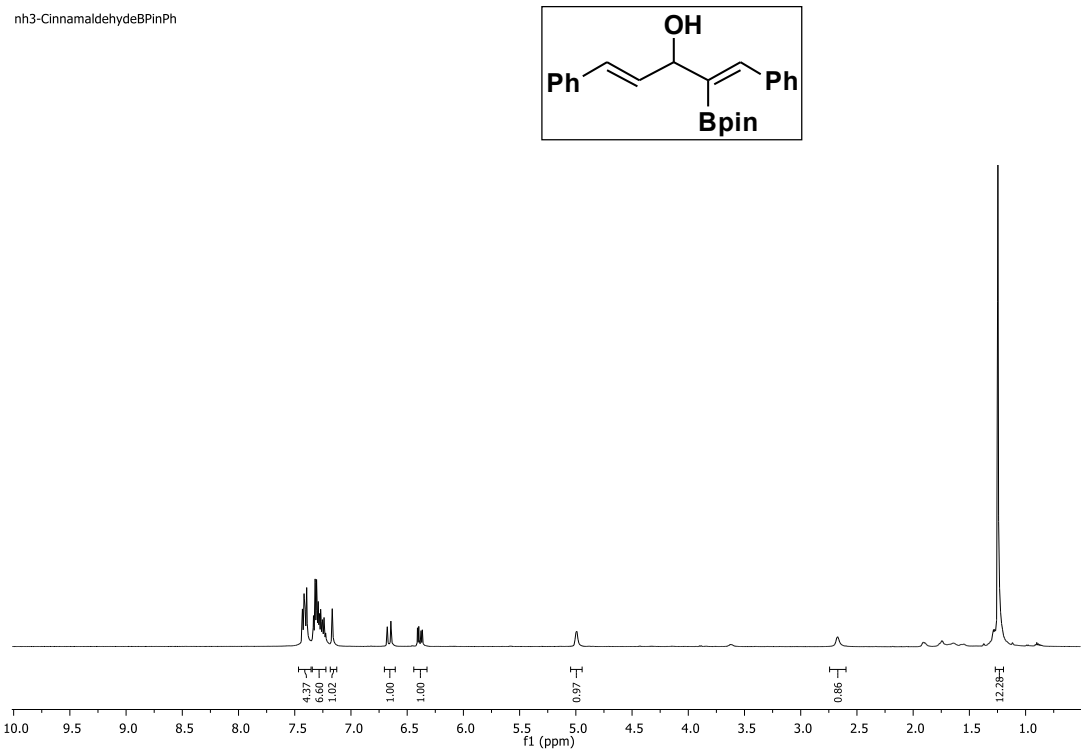


Figure S7 **(1q).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of (1*Z*,4*E*)-2-bromo-1,5-diphenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-1,4-dien-3-ol in $CDCl_3$.



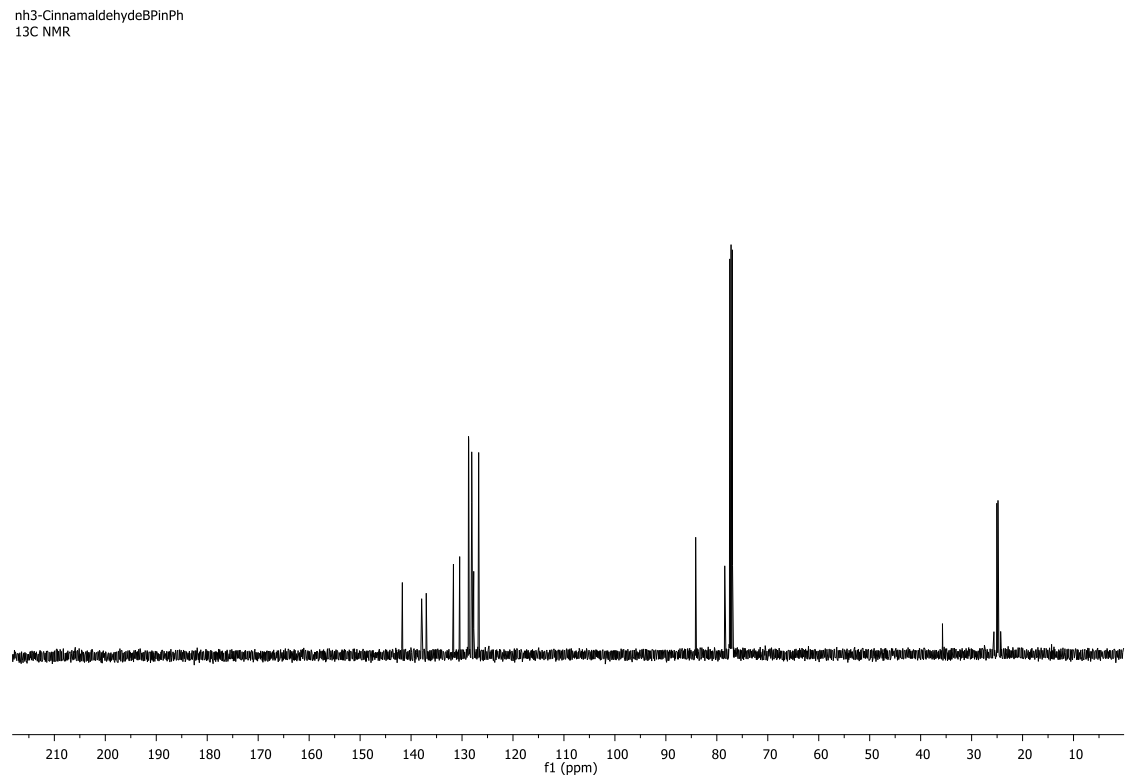


Figure S8 **(1r).** 500 MHz ^{1}H and 125 MHz ^{13}C{^{1}H} NMR of (1*E*,4*E*)-1,5-diphenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-1,4-dien-3-ol in $CDCl_3$.

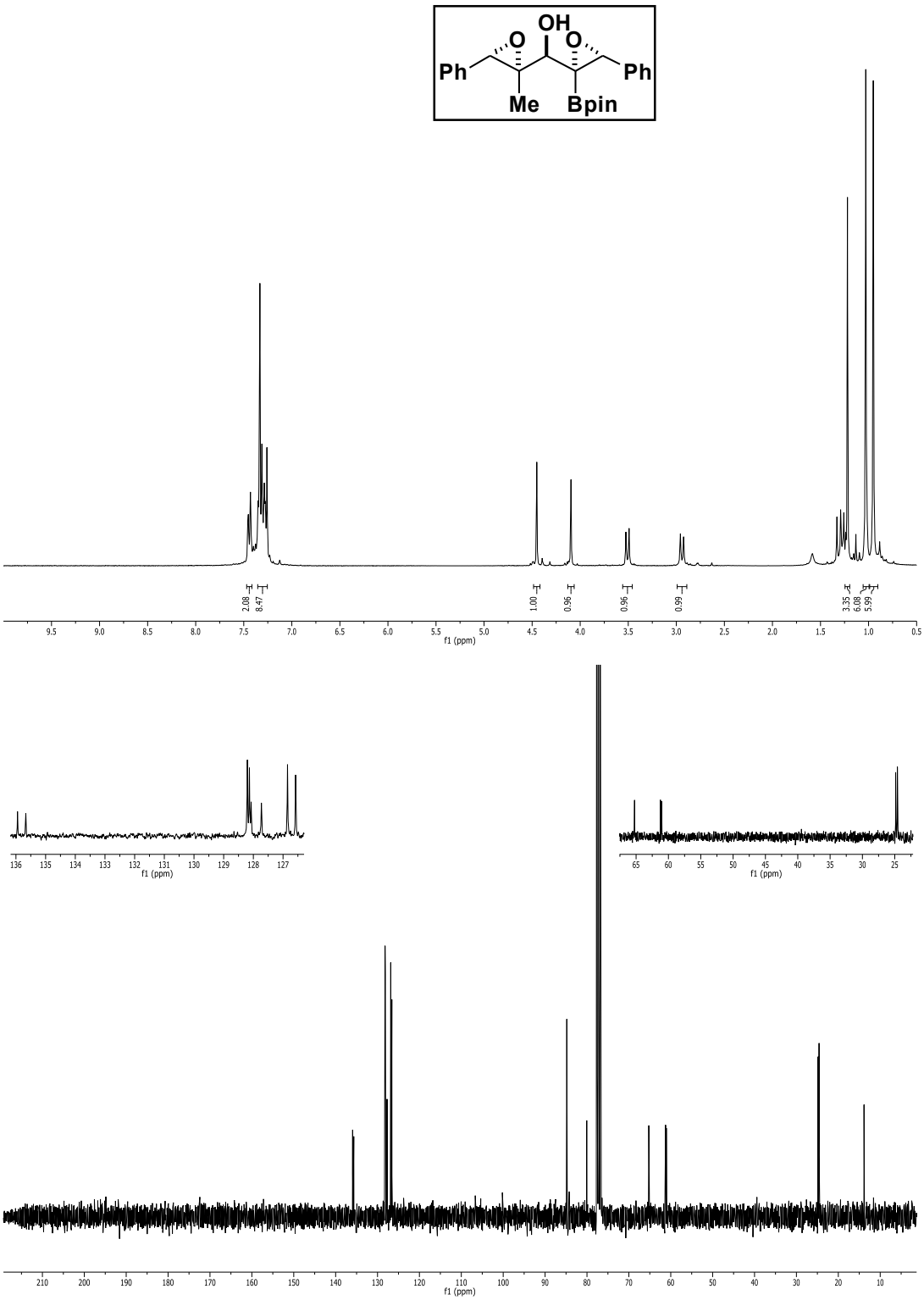


Figure S9 **(2k).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of (2-methyl-3-phenyloxiran-2-yl)(3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methanol in $CDCl_3$.

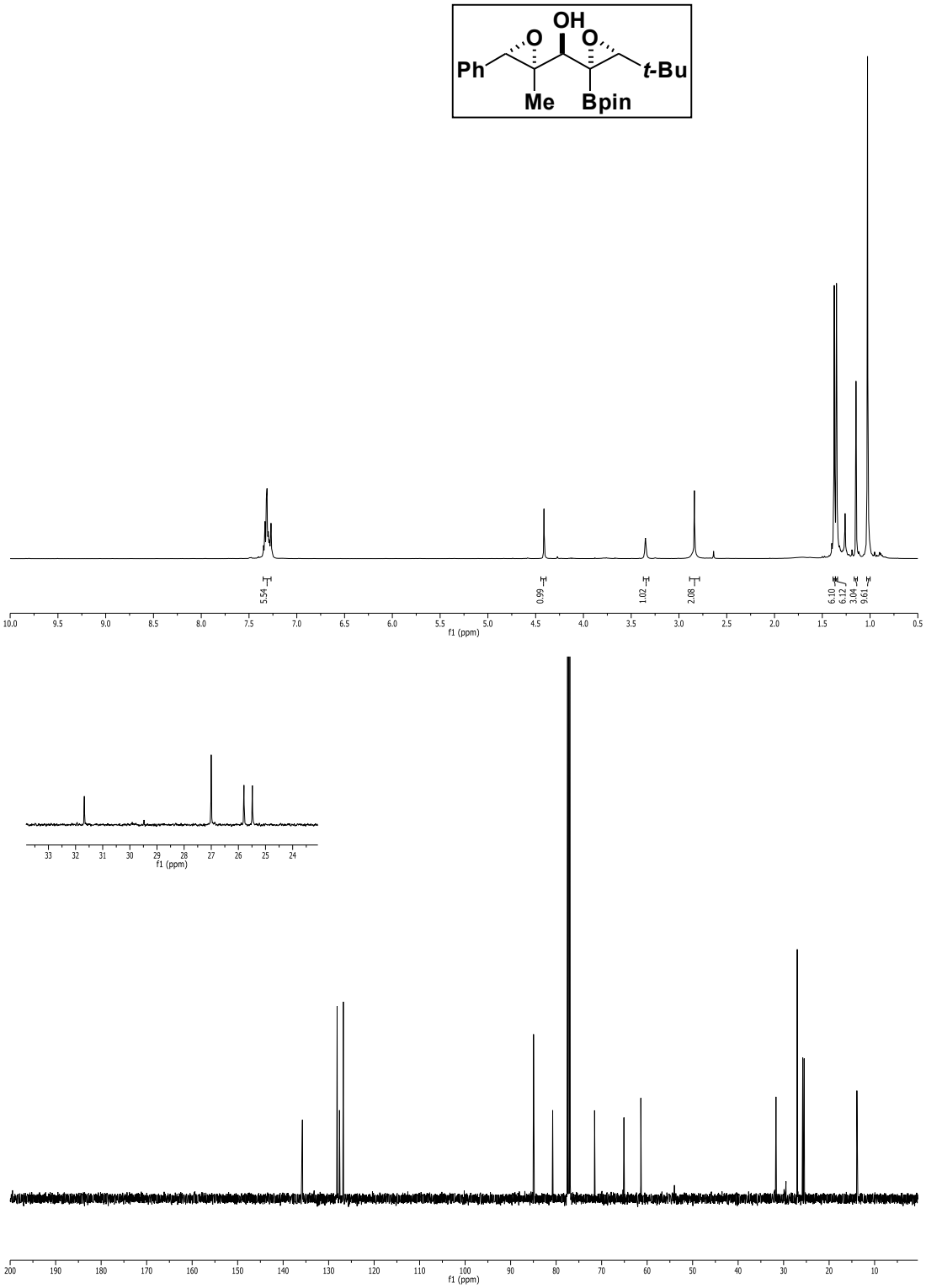


Figure S10 **(2l).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of (3-*tert*-butyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)(2-methyl-3-phenyloxiran-2-yl)methanol in $CDCl_3$.

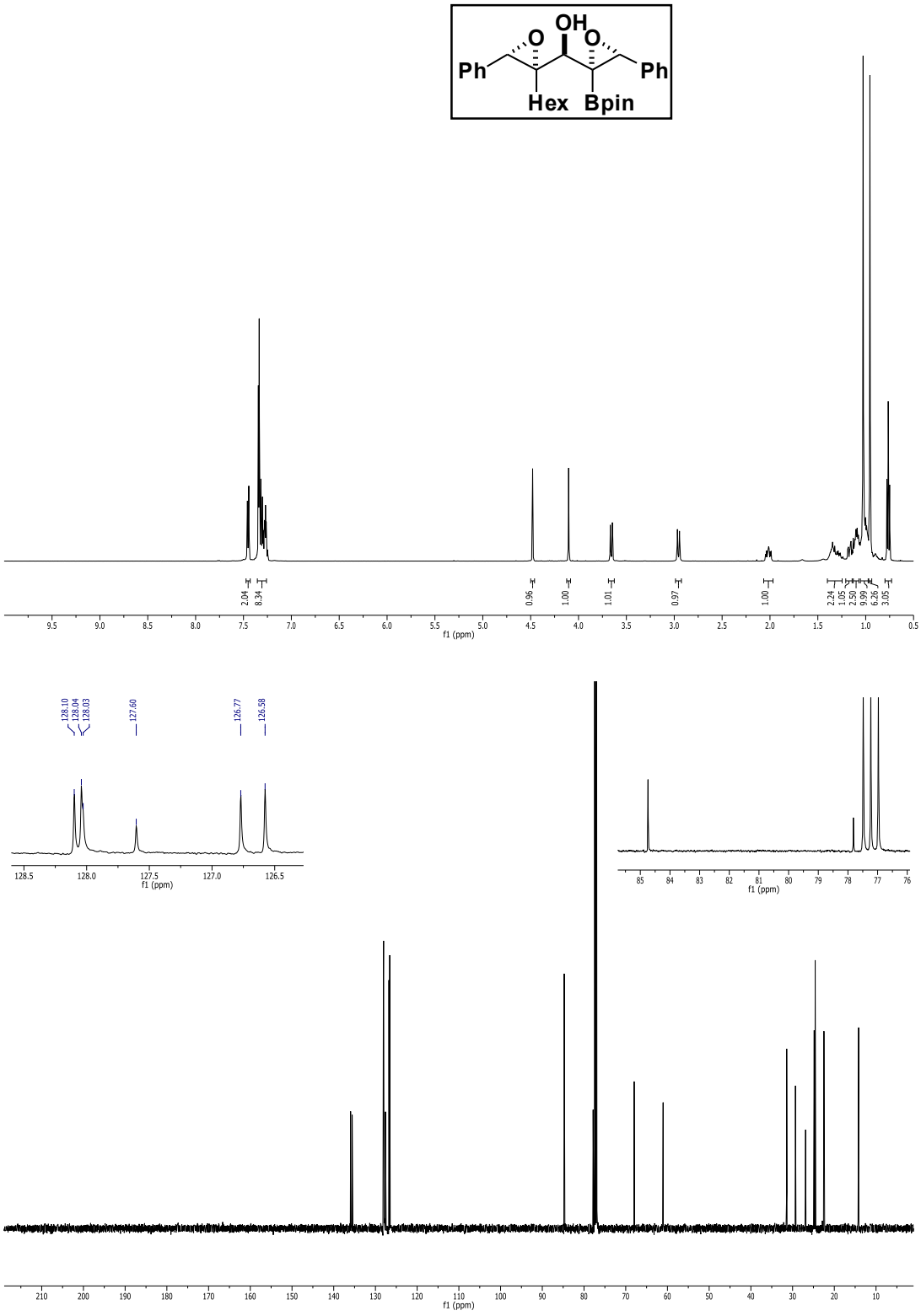


Figure S11 **(2m).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of (2-hexyl-3-phenyloxiran-2-yl)(3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxiran-2-yl)methanol in $CDCl_3$.

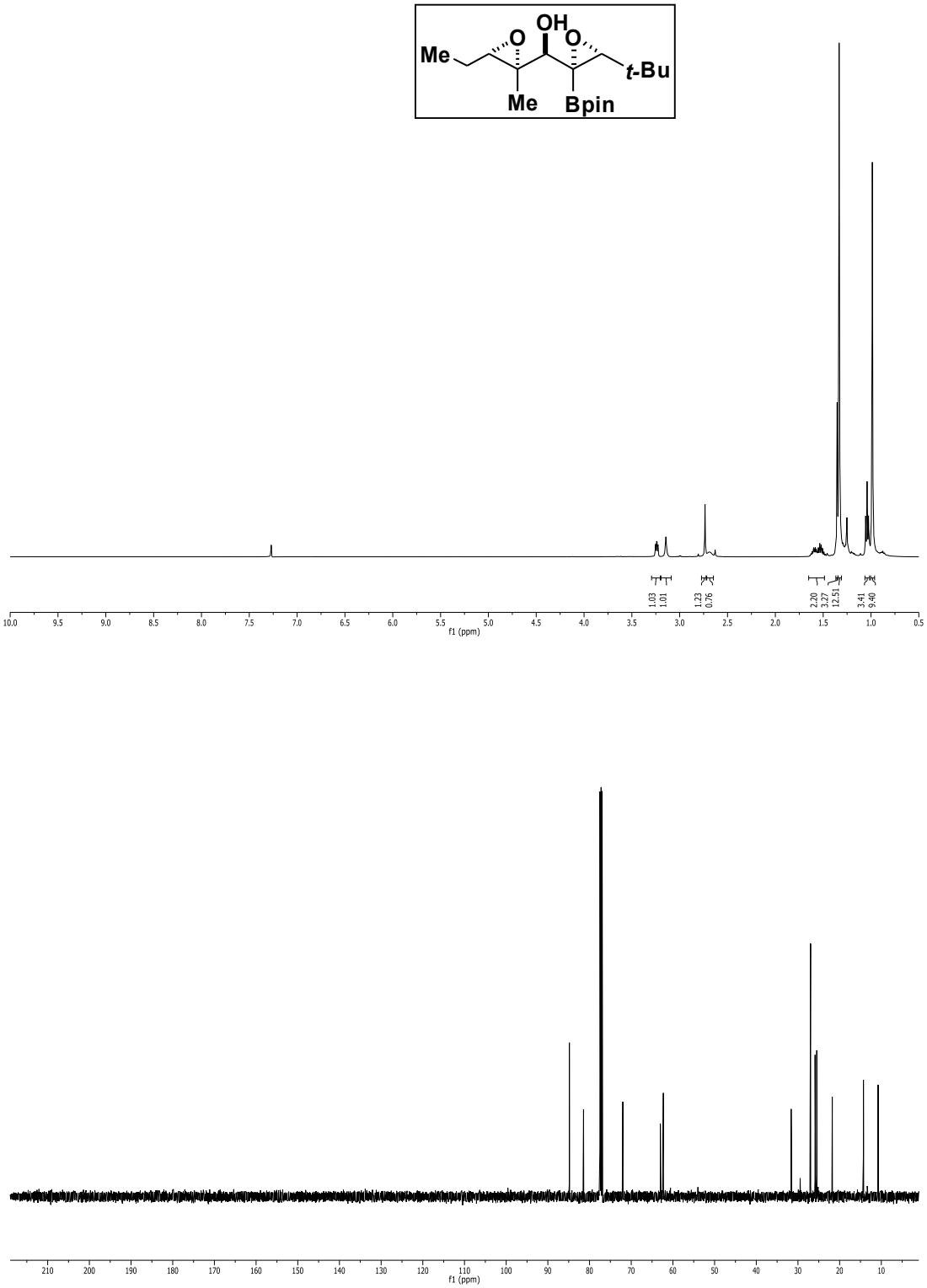


Figure S12 **(2n).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H$ NMR (3-(*tert*-butyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxiran-2-yl)(3-ethyl-2-methyloxiran-2-yl)methanol in $CDCl_3$.

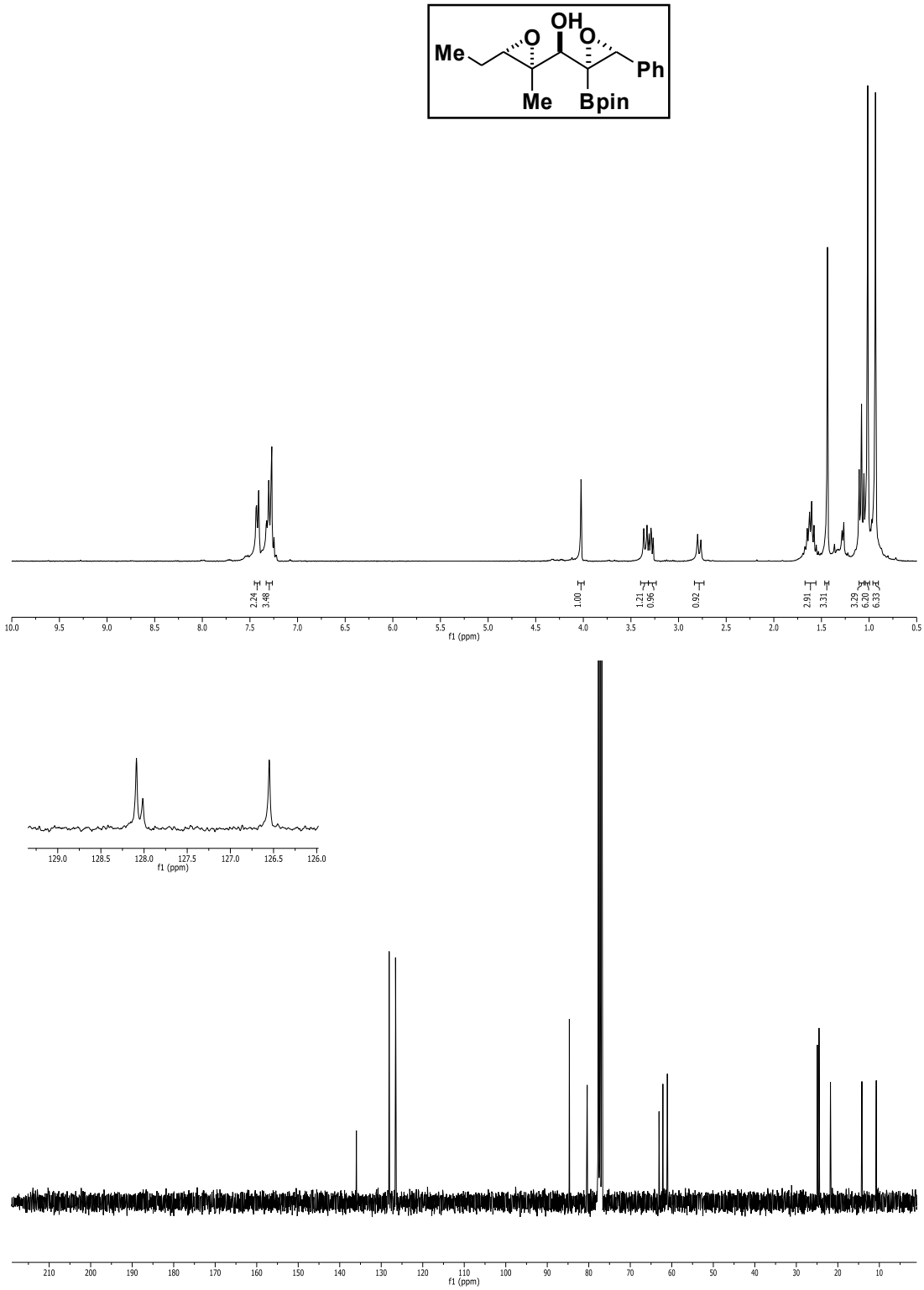


Figure S13 **(2o).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of (3-ethyl-2-methyl-2-methyloxiran-2-yl)(3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methanol in $CDCl_3$.

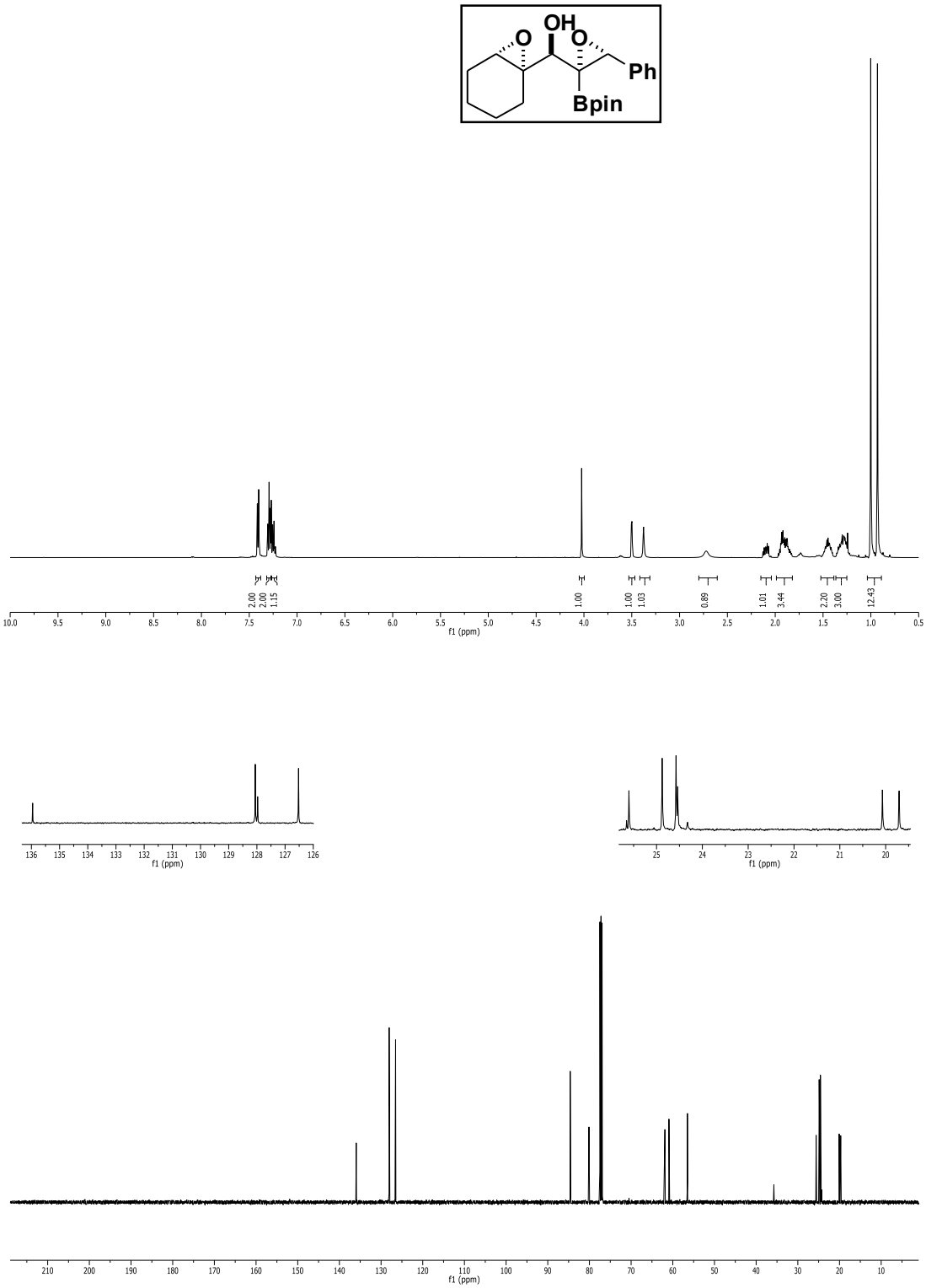


Figure S14 **(2p).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of (7-oxabicycloheptan-1-yl)(3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxiran-2-yl)methanol in $CDCl_3$.

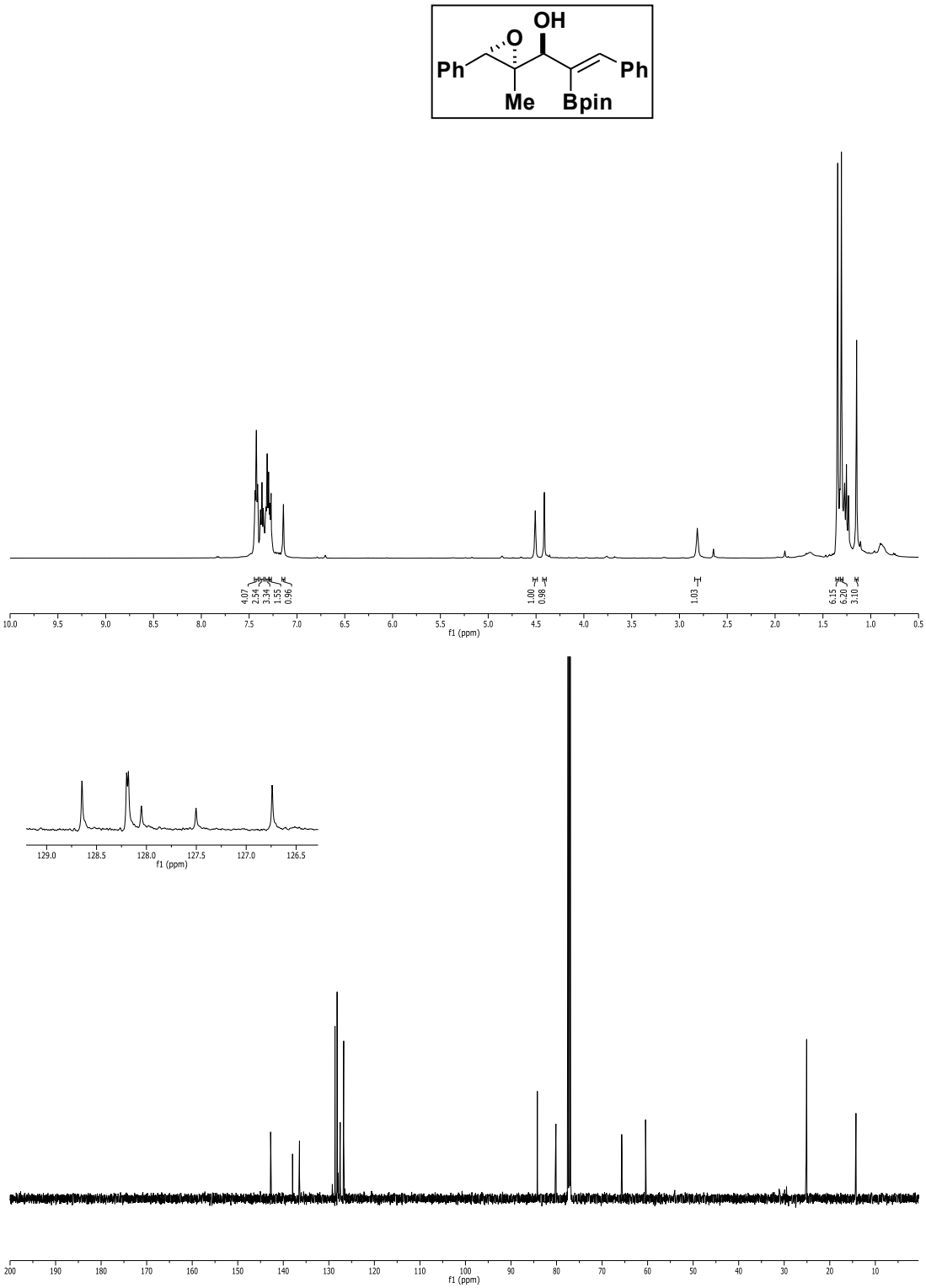


Figure S15 **(3k).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of (*E*)-1-(2-methyl-3-phenyloxiran-2-yl)-3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-en-1-ol in $CDCl_3$.

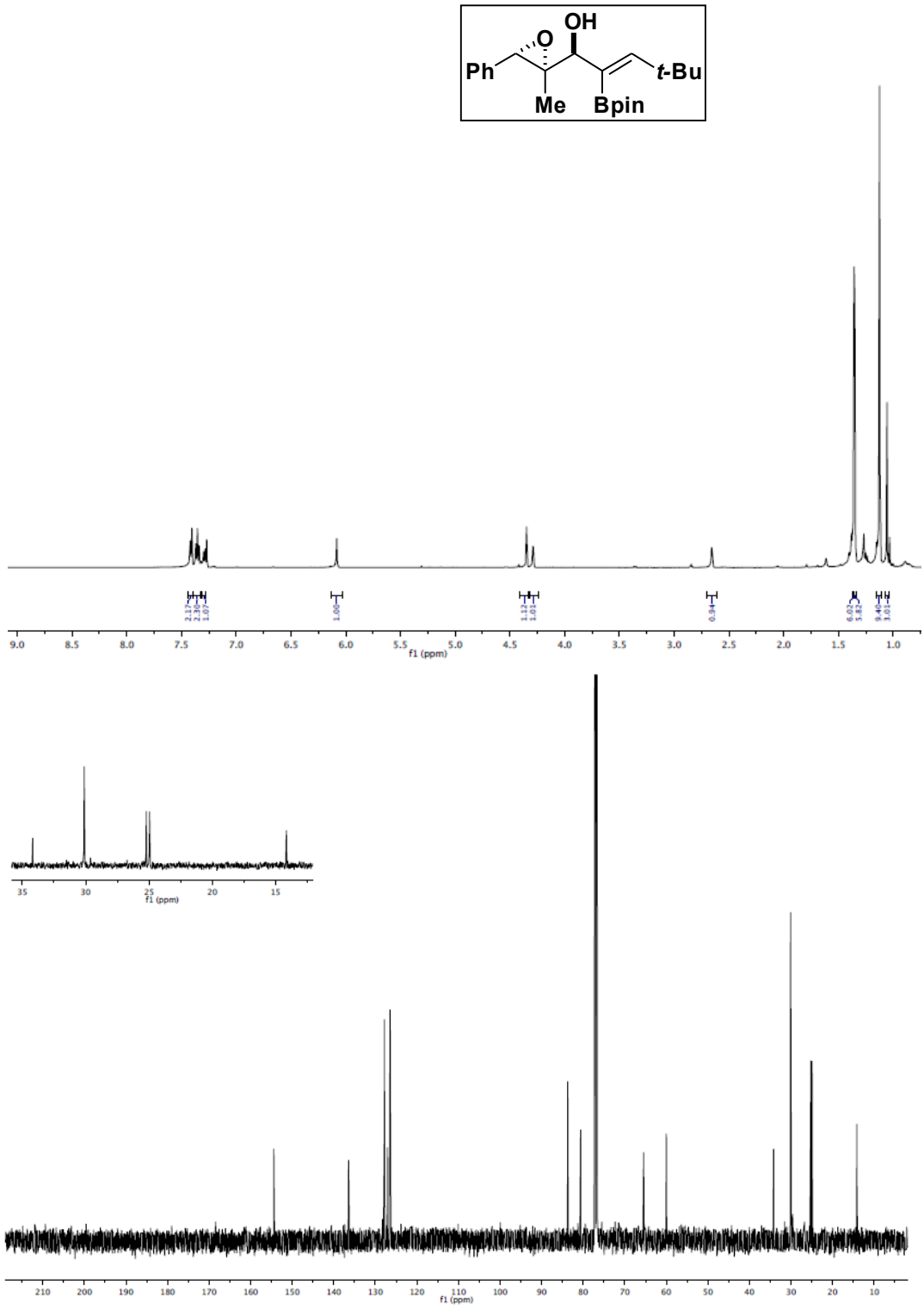


Figure S16 **(3l).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of (*E*)-4,4-dimethyl-1-(2-methyl-3-phenyloxiran-2-yl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-en-1-ol in $CDCl_3$.

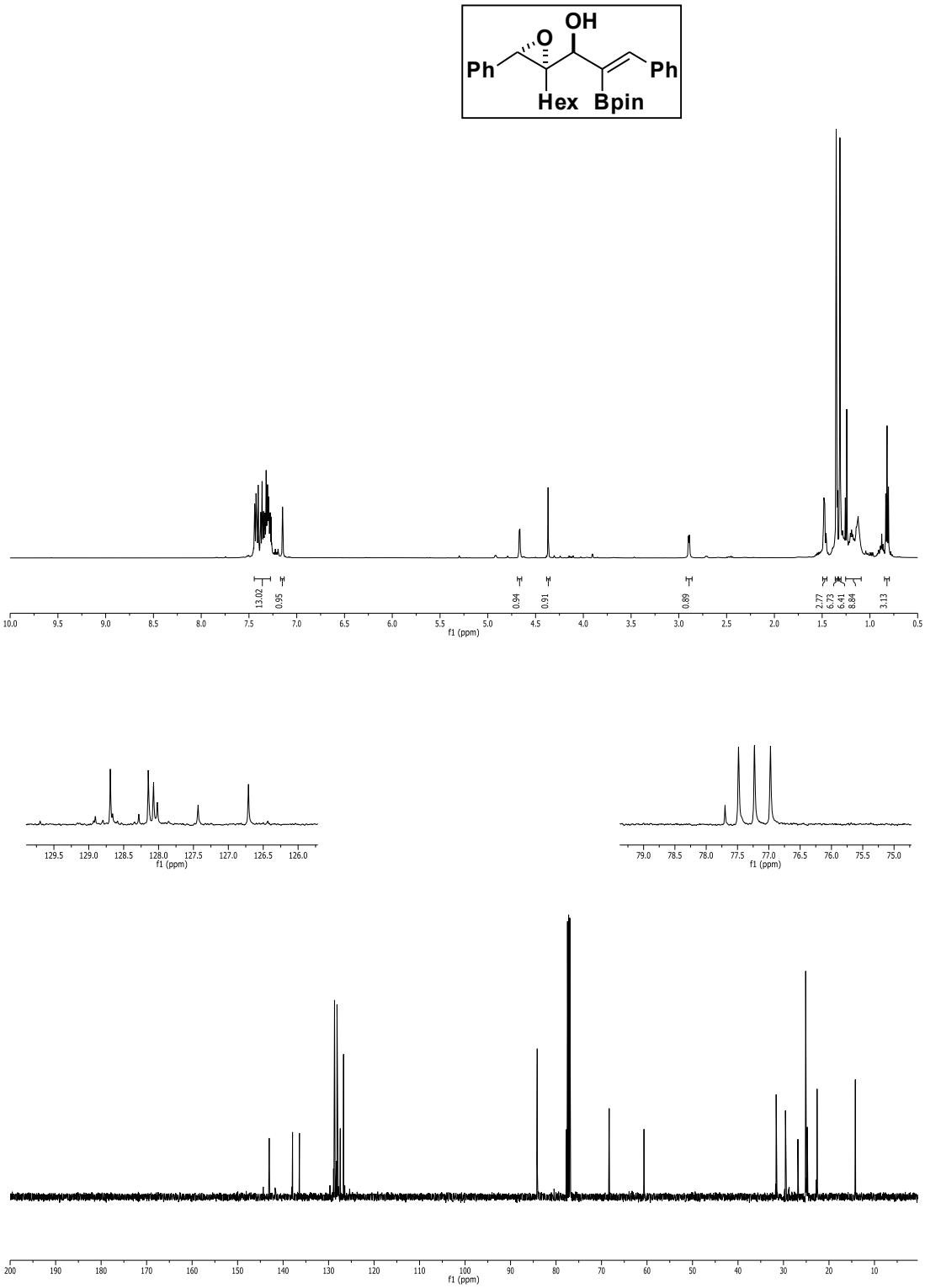


Figure S17 **(3m).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of (*E*)-1-(2-hexyl-3-phenyloxiran-2-yl)-3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-en-1-ol in $CDCl_3$.

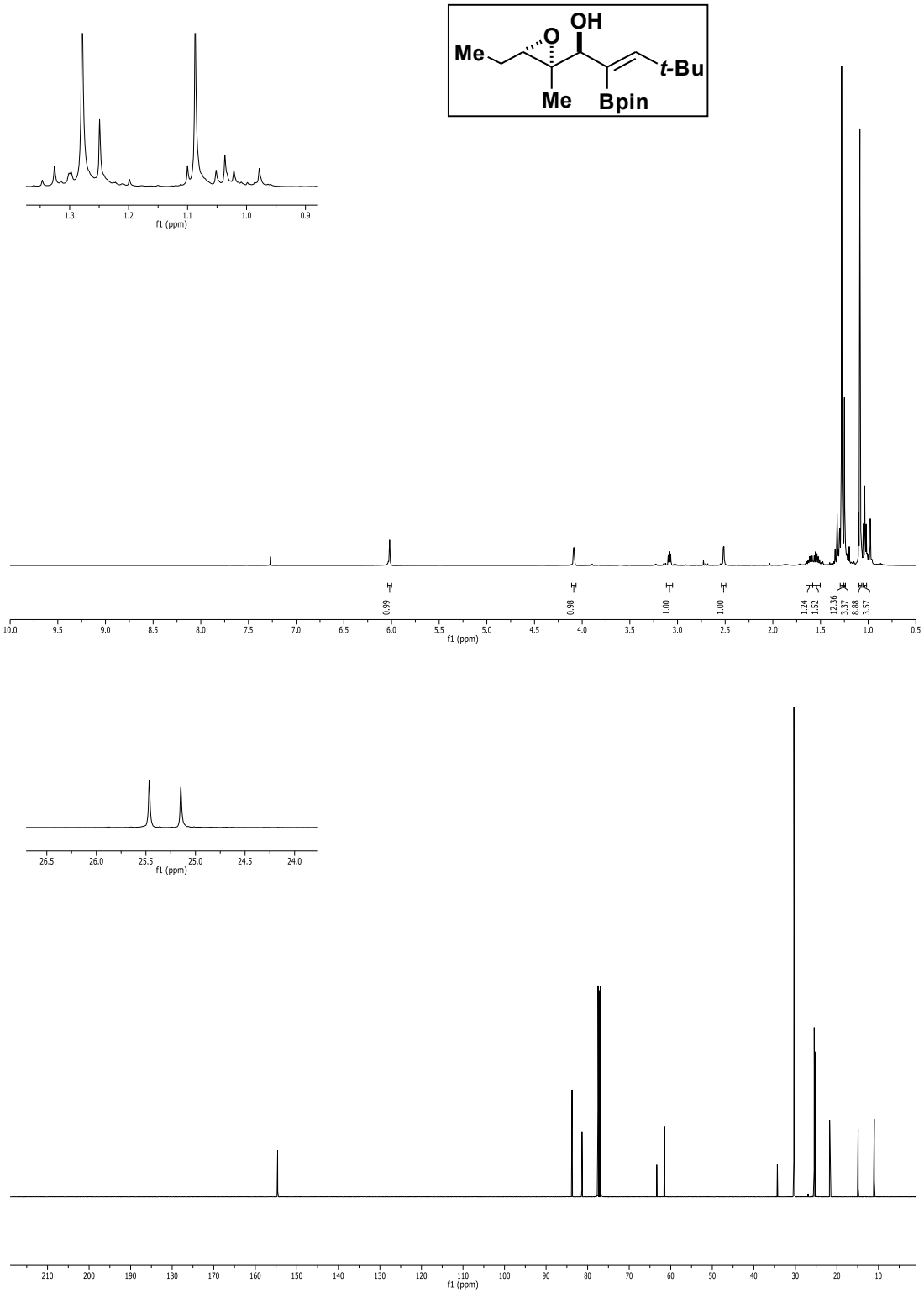


Figure S18 **(3n).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of (*E*)-1-(3-ethyl-2-methyloxiran-2-yl)-4,4--dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-en-1-ol in $CDCl_3$.

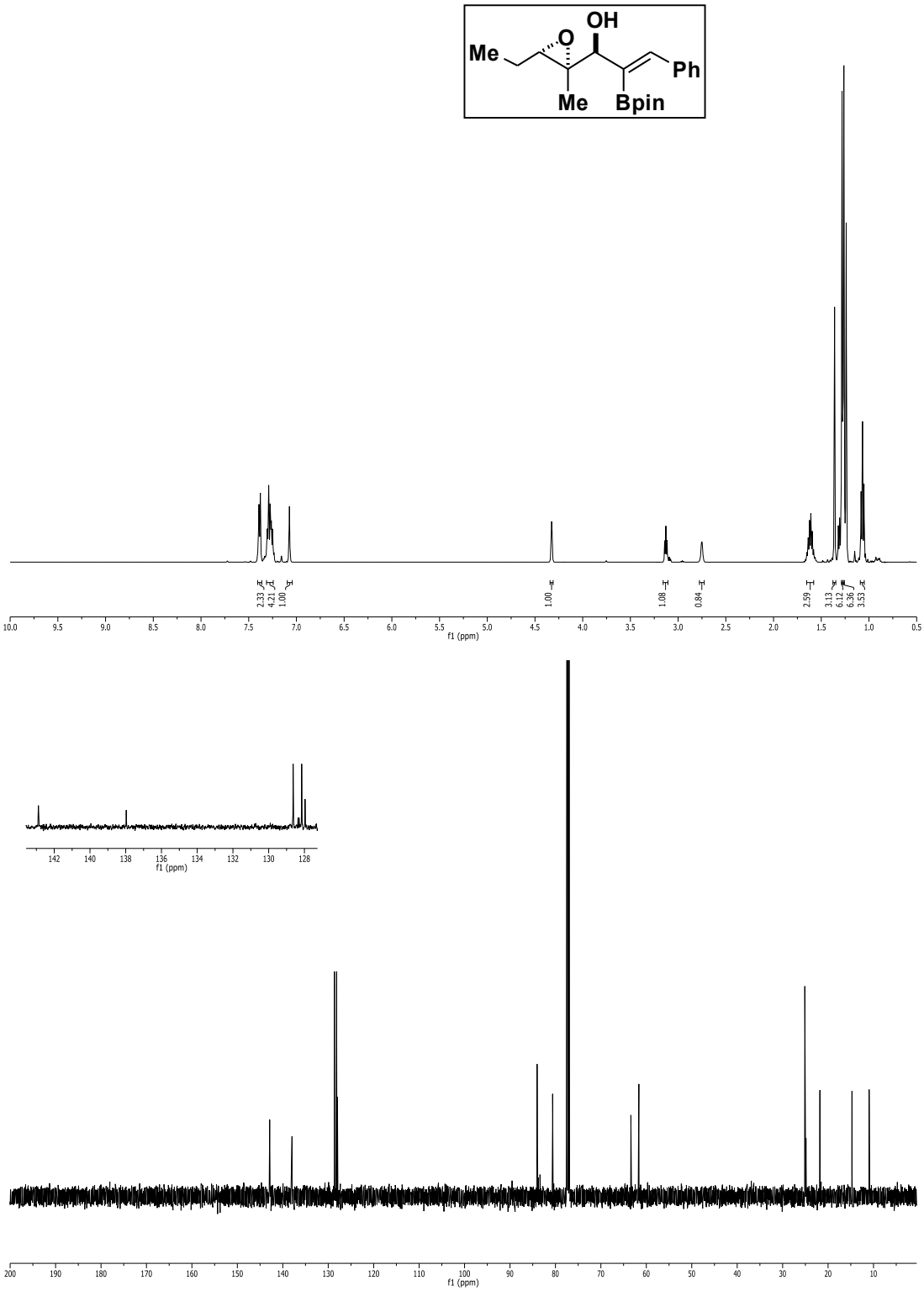


Figure S19 **(3o).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of (E)-1-(3-ethyl-2-methyloxiran-2-yl)-3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-en-1-ol in $CDCl_3$.

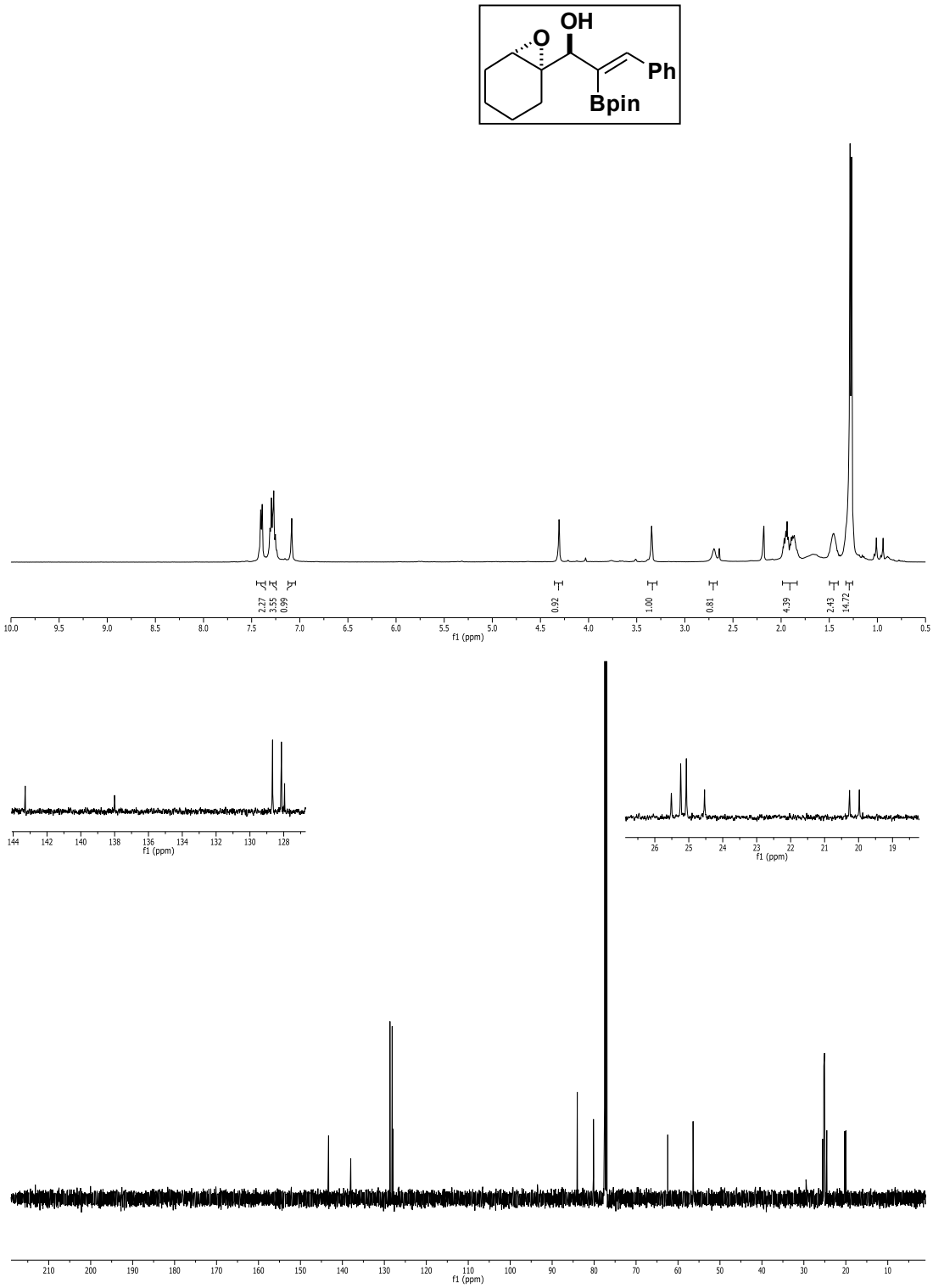


Figure S20 **(3p).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of (E)-1-(7-oxabicyclo heptan-1-yl)-3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-en-1-ol in $CDCl_3$.

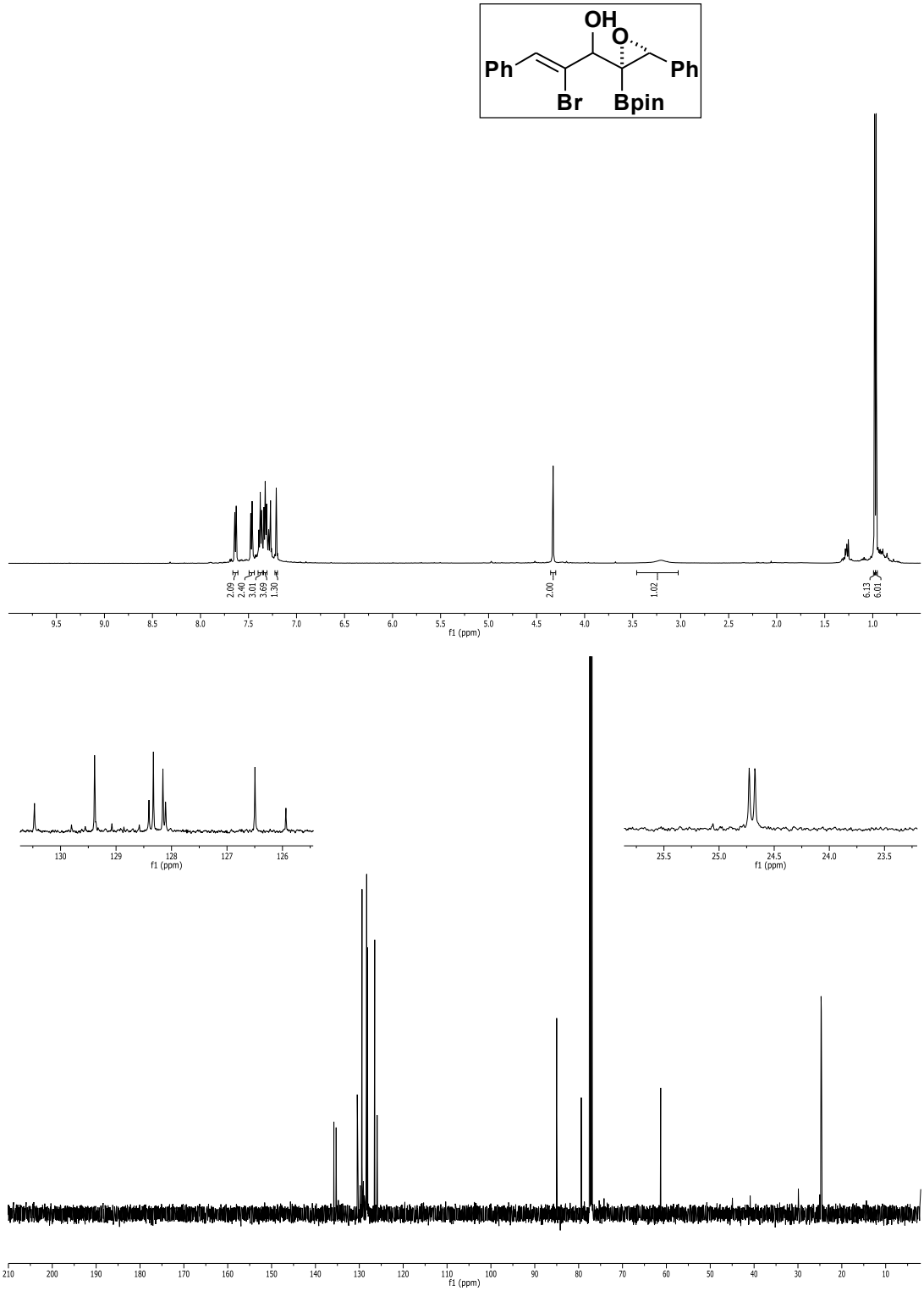
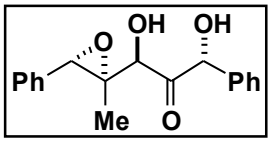


Figure S21 **(4q).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of (Z)-2-bromo-3-phenyl-1-(3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxiran-2-yl)prop-2-en-1-olin $CDCl_3$.



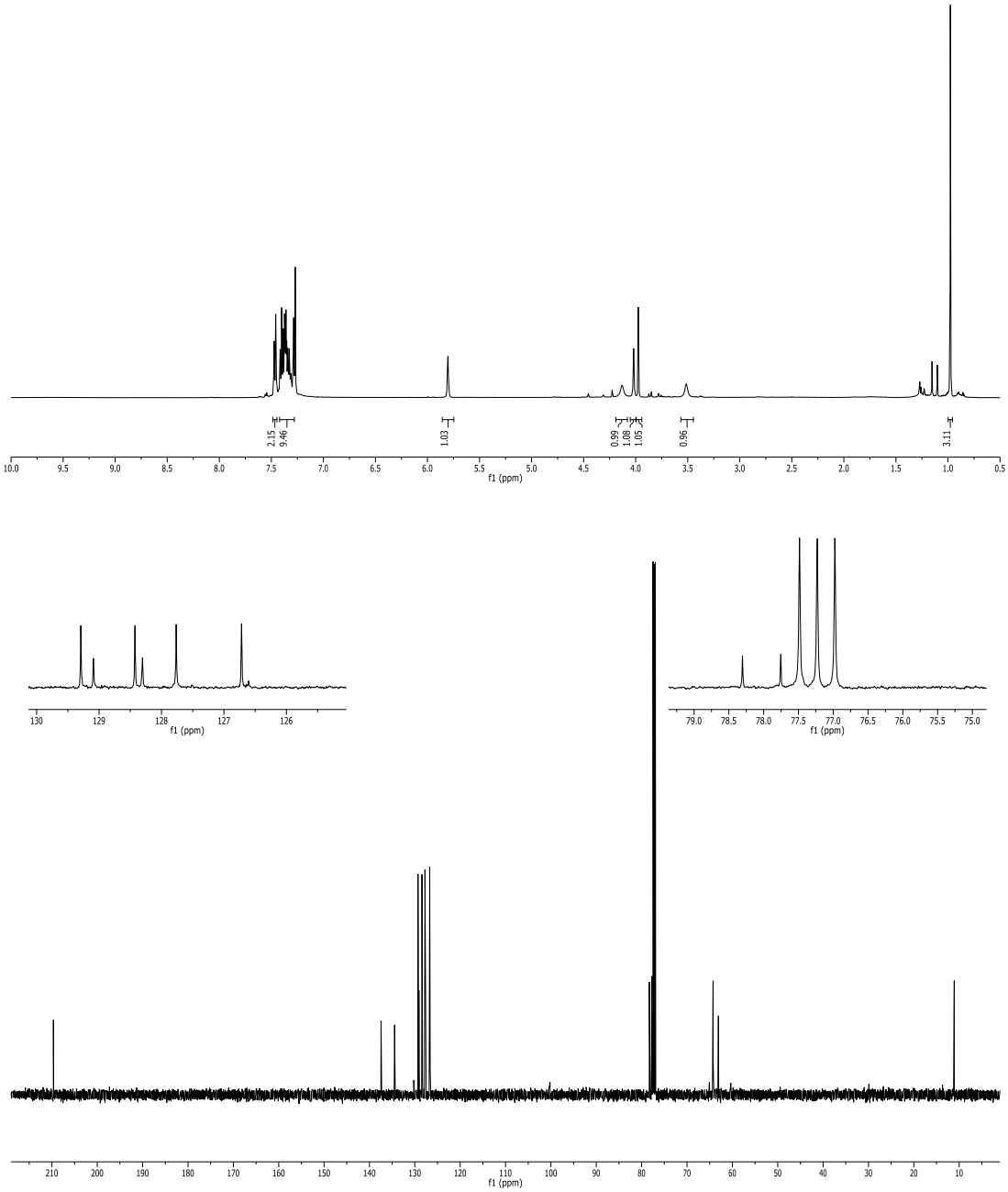


Figure S22 **(5k).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 1,3-dihydroxyl-1-(2-methyl-3-phenyloxiran-2-yl)-3-phenylpropan-2-one in $CDCl_3$.

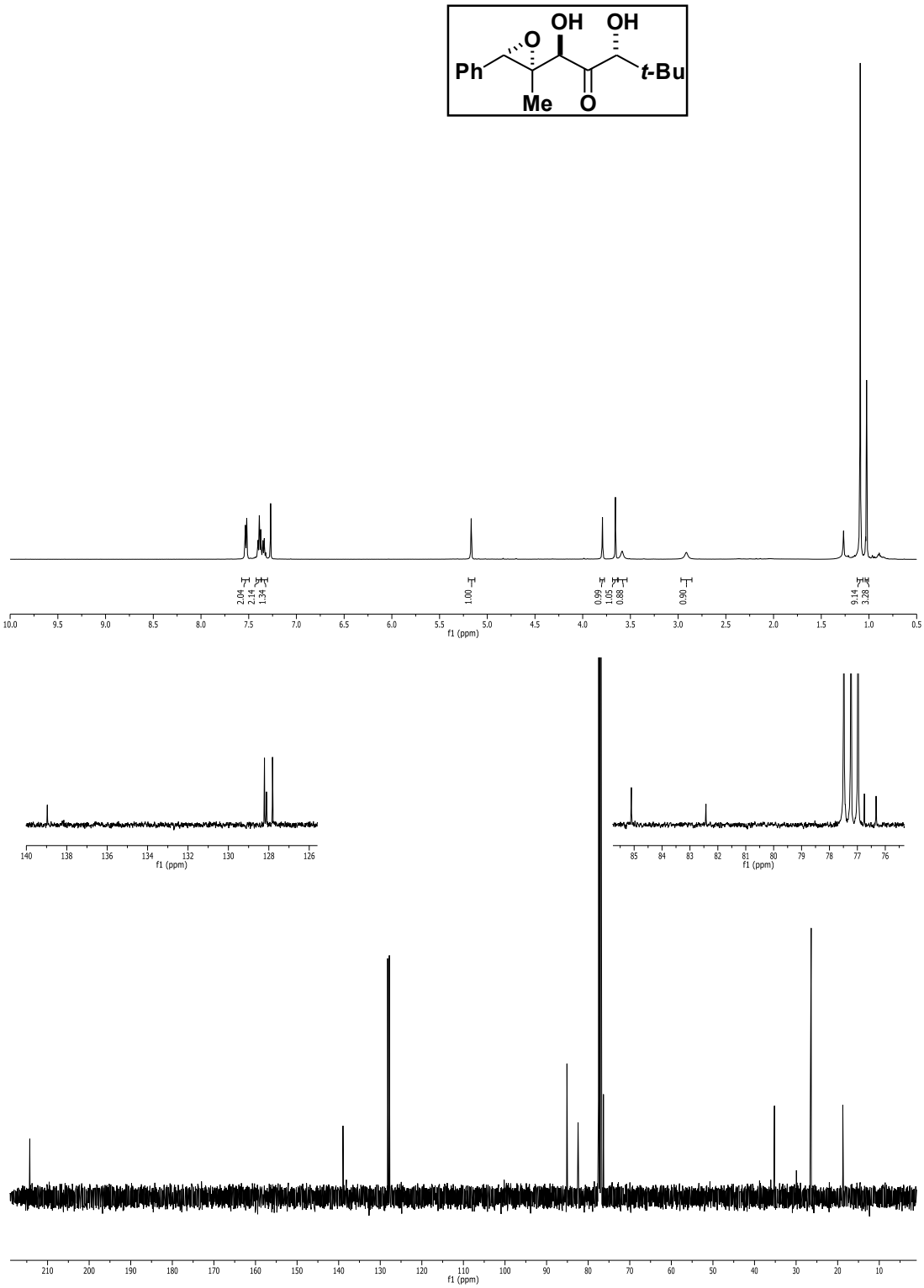
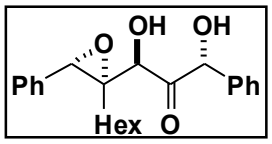


Figure S23 **(5l).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 1,3-dihydroxy-4,4-dimethyl-1-(2-methyl-3-phenyloxiran-2-yl)pentan-2-one in $CDCl_3$.



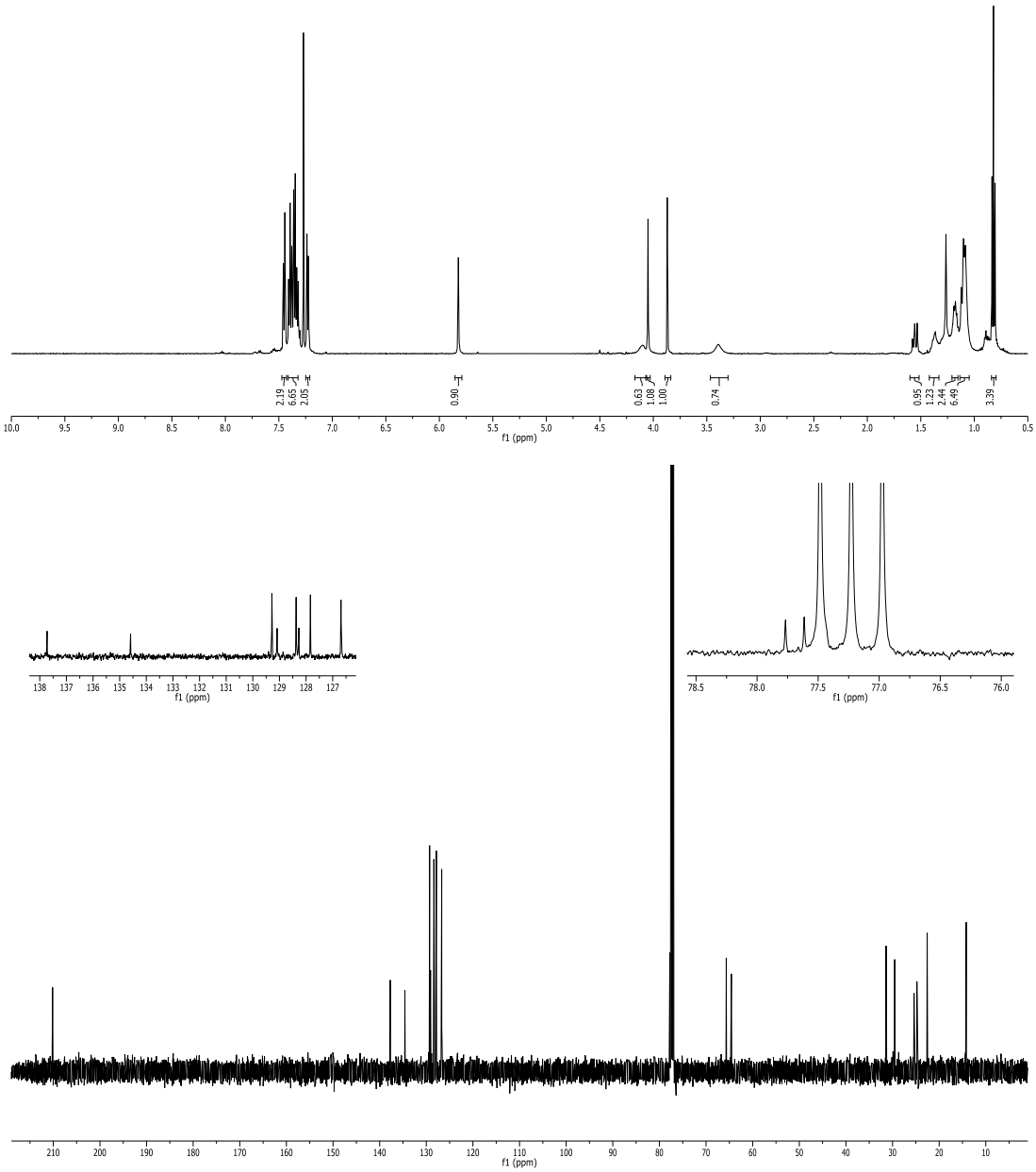


Figure S24 **(5m).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 1-(2-hexyl-3-phenyloxiran-2-yl)-1,3-dihydroxy-3-phenylpropan-2-one in $CDCl_3$.

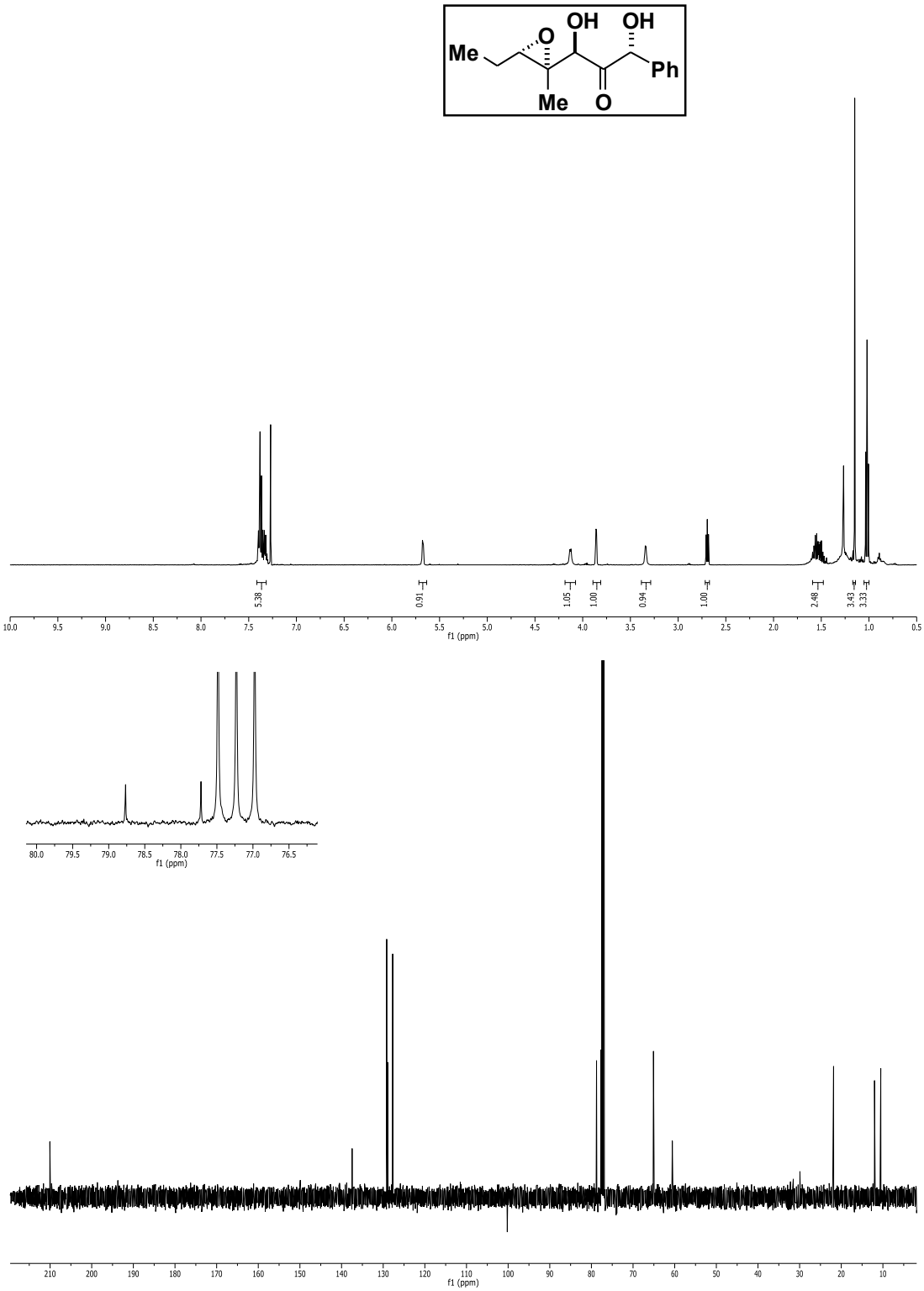


Figure S25 **(5o).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 1-(3-ethyl-2-methyloxiran-2-yl)-1,3-dihydroxy-3-phenylpropan-2-one in $CDCl_3$.

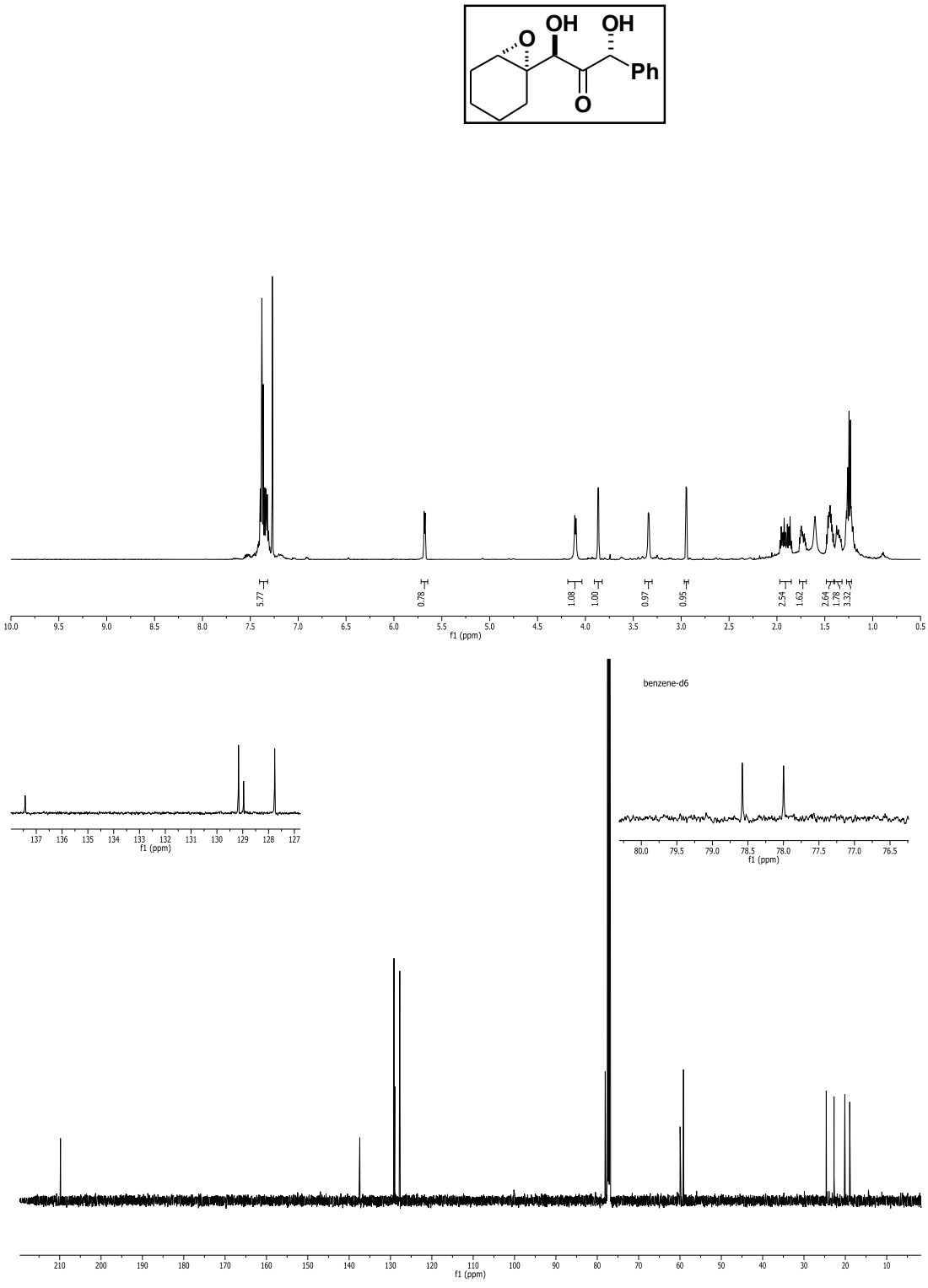


Figure S26 **(5p).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 1-(7-oxabicycloheptan-1-yl)-1,3-dihydroxy-3-phenylpropan-2-one in $CDCl_3$.

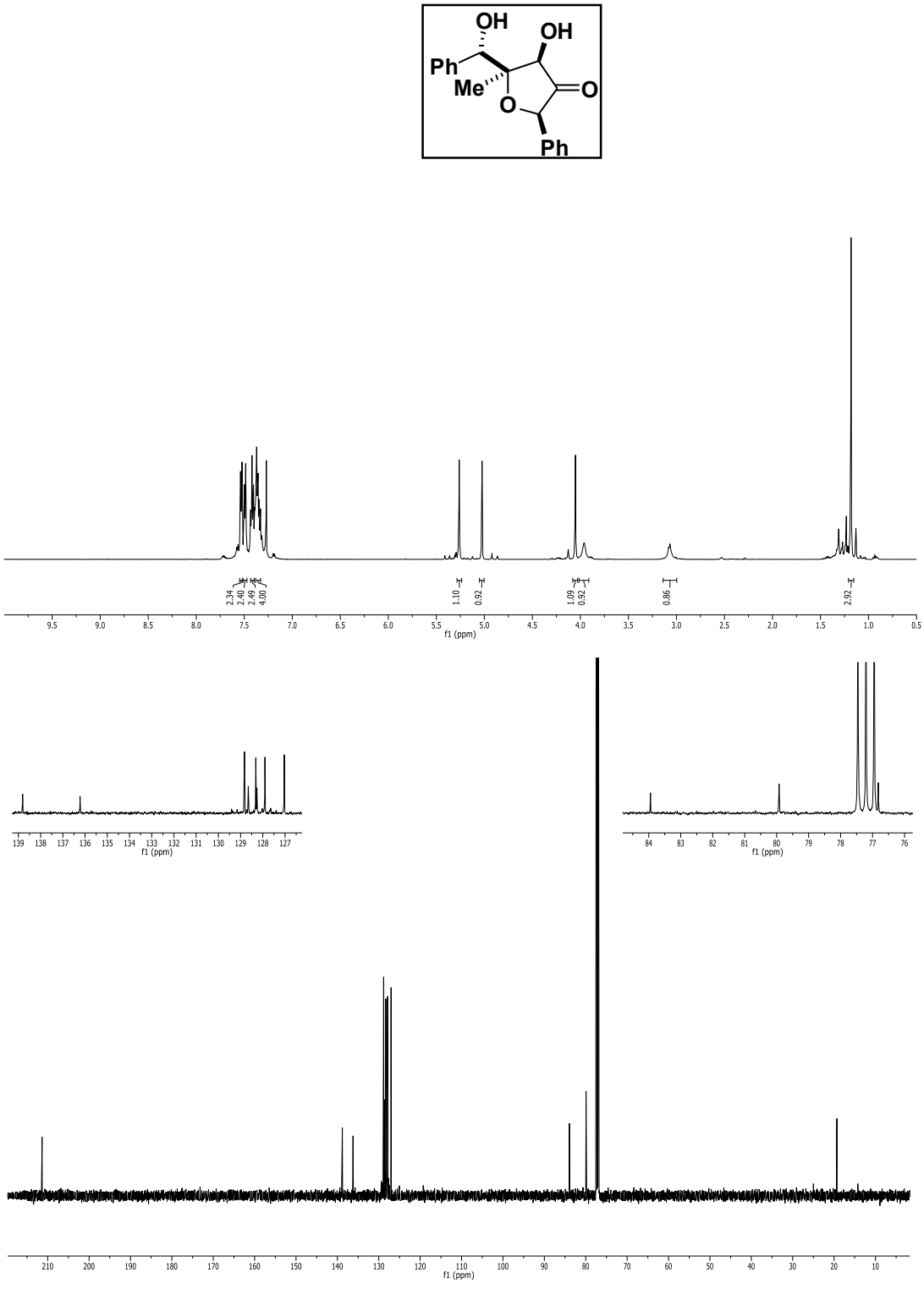
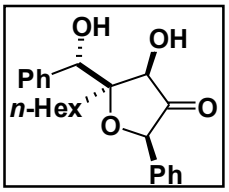
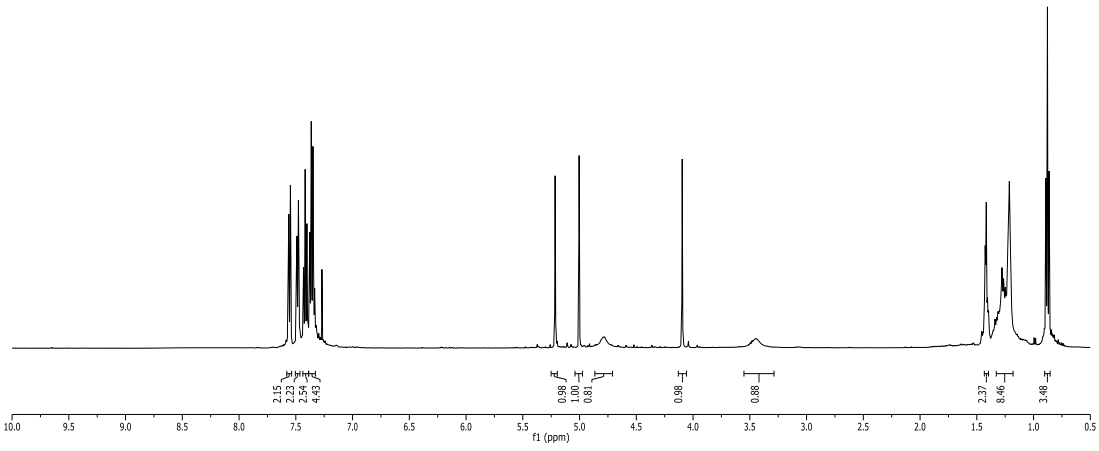


Figure S27 **(6k).** 500 MHz ^{1}H and 125 MHz ^{13}C{^{1}H} NMR of 4-hydroxy-5-(hydroxyl(phenyl)methyl)-5-methyl-2-phenyldihydrofuran-3-(2*H*)-one in $CDCl_3$.





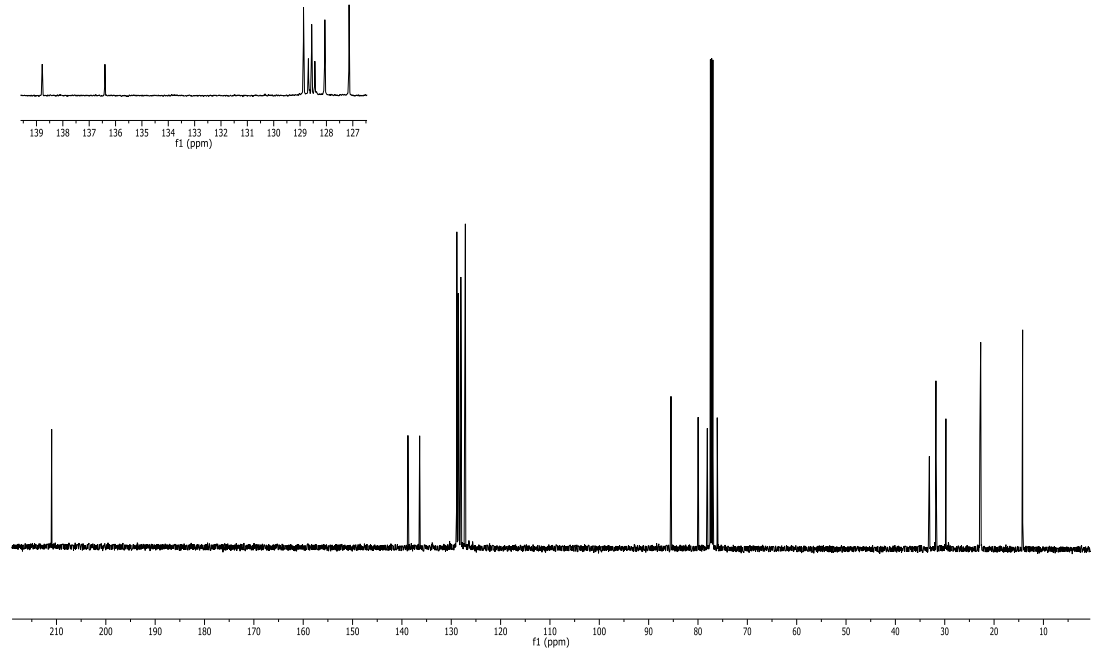


Figure S28 **(6m).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 5-hexyl-4-hydroxy-5-(hydroxyl(phenyl)methyl-2-phenyldihydrofuran-3-2(H)-one in $CDCl_3$.

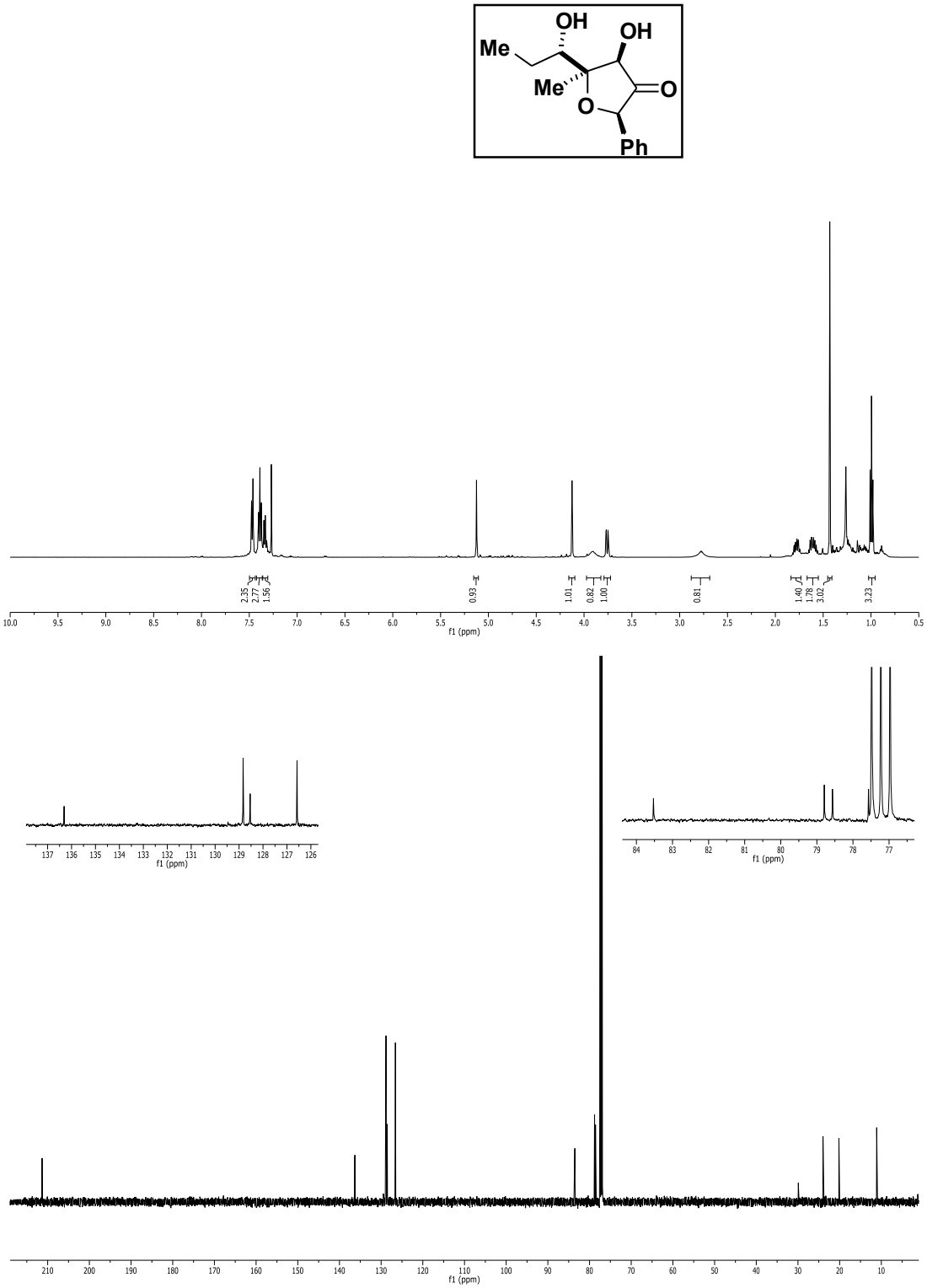


Figure S29 **(6o).** 500 MHz ^{1}H and 125 MHz ^{13}C{^{1}H} NMR of 4-hydroxy-5-(1-hydroxypropyl)-5-methyl-phenyldihydrofuran-3(2*H*)-one in $CDCl_3$.

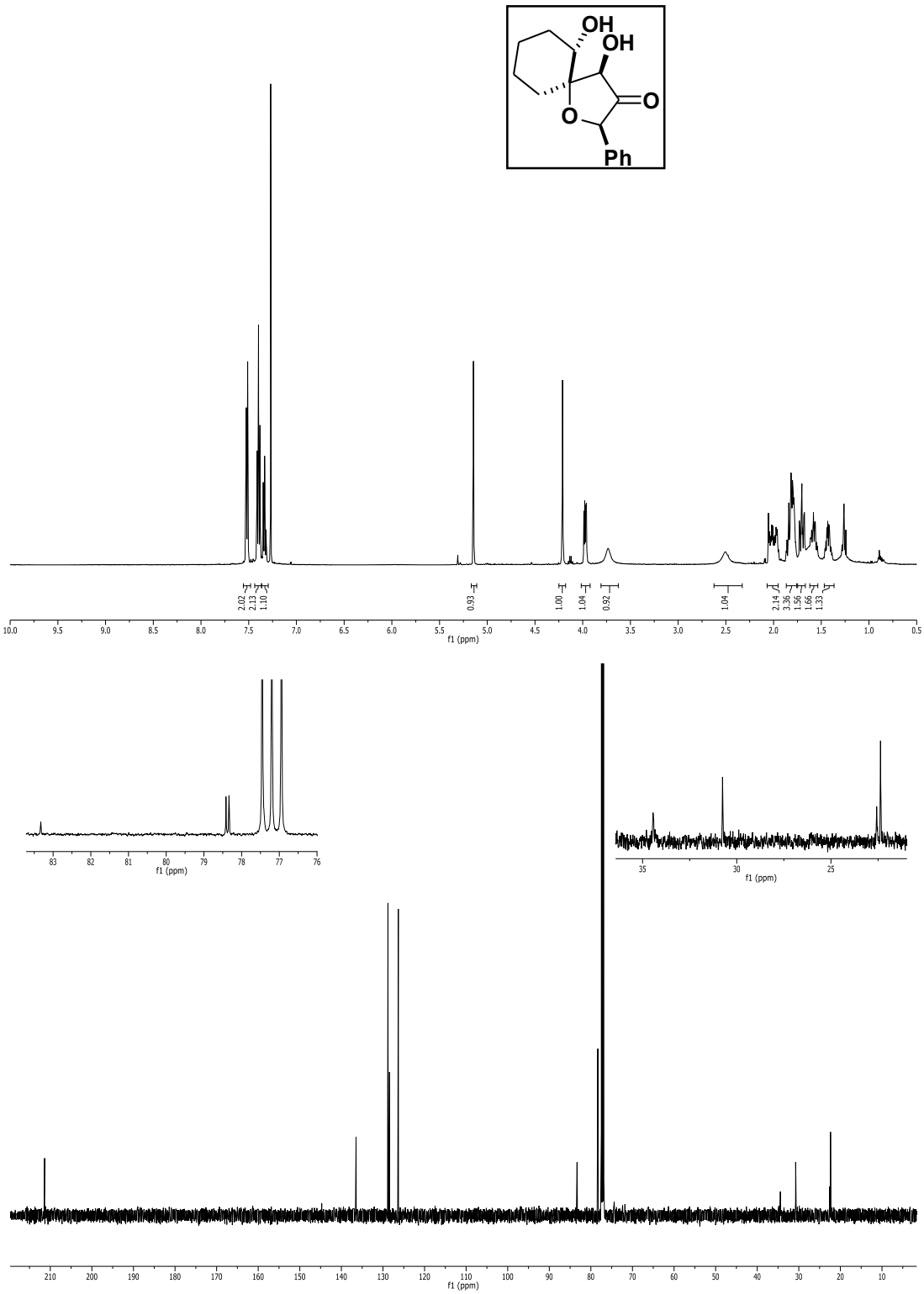


Figure S30 **(6p).** 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of 4,6-dihydroxy-2-phenyl-1-oxaspiro[4,5]decan-3-one in $CDCl_3$.

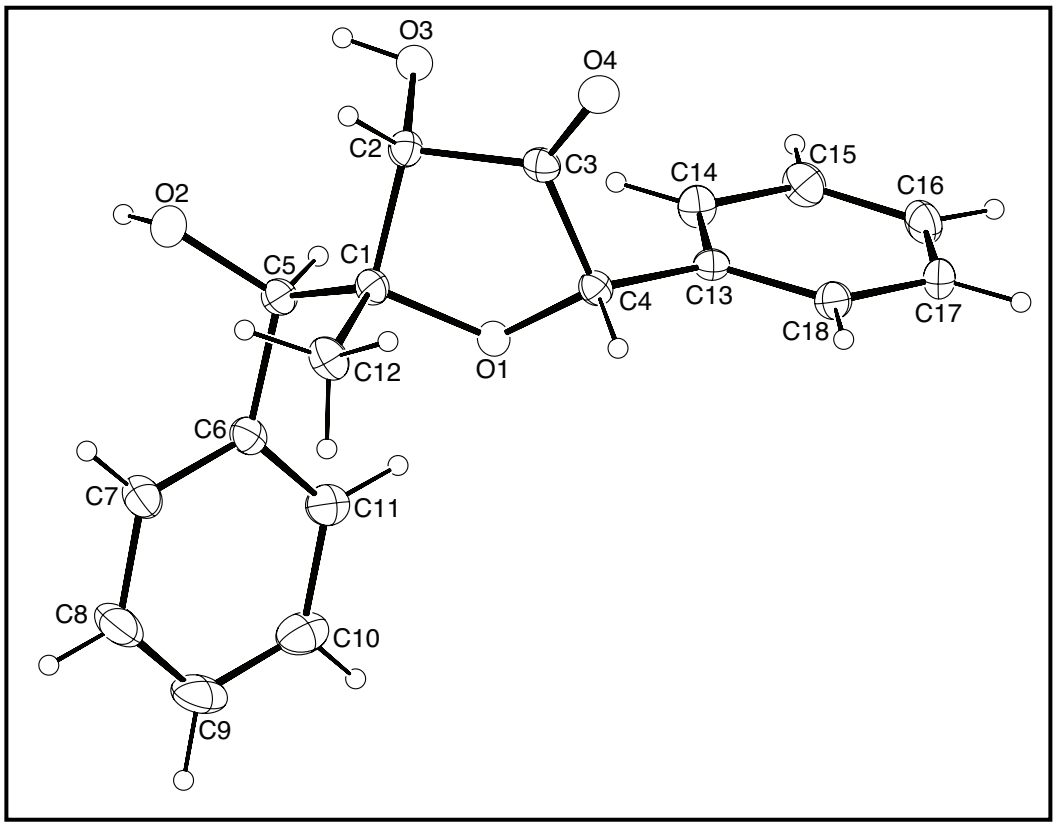


Figure S31**.** ORTEP drawing of 4-hydroxy-5-(hydroxyl(phenyl)methyl)-5-methyl-2-phenyldihydrofuran-3-(2*H*)-one (**6k**) with 30% probability thermal ellipsoids.

Preliminary Computational Studies:

All calculations were optimized using *GAUSSIAN09*[1], B3LYP[2-5] or M06-2X[6, 7] functional with the 6-31G(d) or 6-311G(d,p), basis set in the gas phase and in dichloromethane using CPCM[8] solvation model and UFF radii.[9-11] Optimizing transition state structures using (U)B3LYP with guess=(mix, always) did not revealed any changes in spin state. Frequency analysis was used to characterize each stationary point as minima or transition state structure. Further, IRC[12, 13] calculations were carried out on model systems to connect transition state structures to minima.

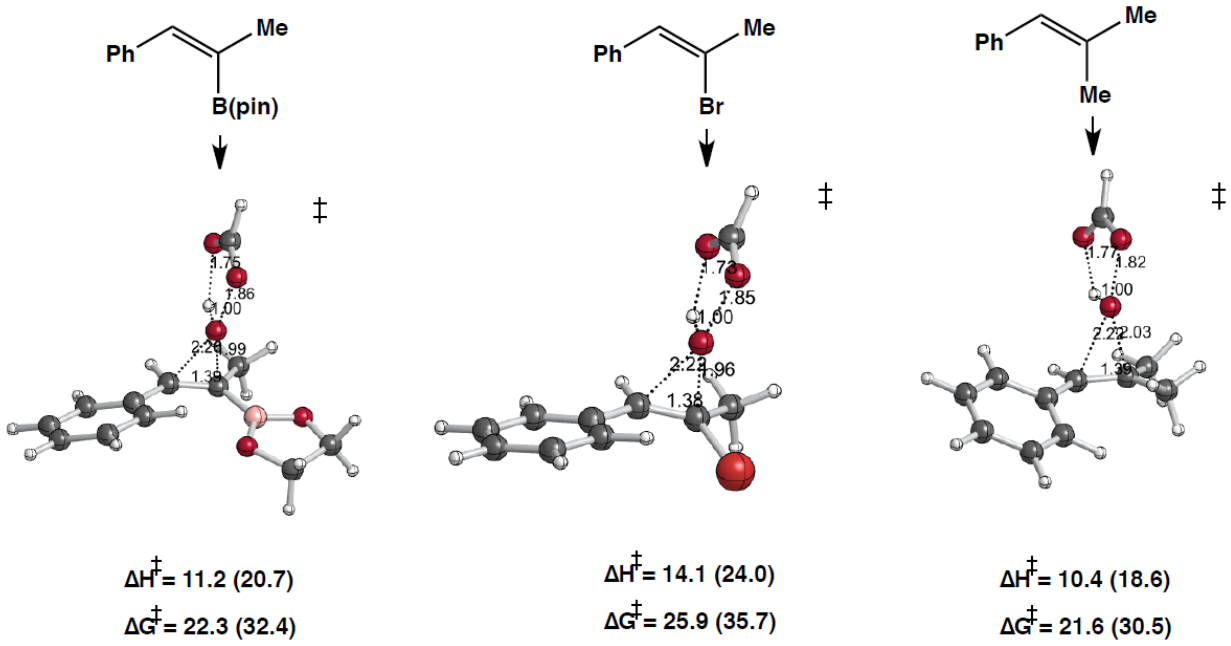


Figure S31**.** Relative barriers for epoxidations of model alkenes. All structures were calulated using B3LYP/6-31G(d) in gas phase and in dichloromethane (CPCM;UFF radii), in parenthesis, using M06-2X/6-311G(d,p). Reported energies are in kcal/mol. Pinacolato ligand was modeled as $C_2H_4O_2$.

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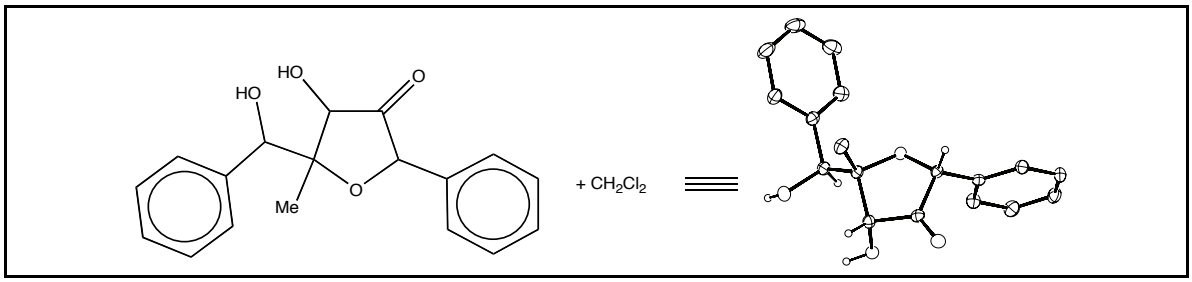
Appendix B X-ray Structure Reports

pwaX-ray Structure Determination of Compound 6181



Compound 6181, $C_{19}H_{20}O_4Cl_2$, crystallizes in the orthorhombic space group $P2_12_12_1$ (systematic absences h00: h=odd, 0k0: k=odd, and 00l: l=odd) with a=7.8057(5)Å, b=10.1854(7)Å, c=23.4262(17)Å, V=1862.5(2)Å^3, Z=4, and d_{calc}=1.367 g/cm^3. X-ray intensity data were collected on a Bruker APEXII CCD area detector employing graphite-monochromated Mo-Kα radiation (λ=0.71073 Å) at a temperature of 143(1)K. Preliminary indexing was performed from a series of thirty-six 0.5° rotation frames with exposures of 10 seconds. A total of 2112 frames were collected with a crystal to detector distance of 37.574 mm, rotation widths of 0.5° and exposures of 30 seconds:

scan type	2θ	ω	ϕ	χ	frames
ϕ	-10.50	335.72	25.44	54.21	739
ω	-10.50	345.67	80.80	-60.33	91
ϕ	19.50	327.79	15.97	36.30	669
ω	17.00	321.08	318.36	83.36	95
ω	-8.00	320.62	277.32	84.61	68
ϕ	-18.00	124.02	292.98	-95.28	450

Rotation frames were integrated using SAINT[i], producing a listing of unaveraged F^2 and $\sigma(F^2)$ values which were then passed to the SHELXTL[ii] program package for further processing and structure solution. A total of 31652 reflections were measured over the ranges $1.74 \leq \theta \leq 25.37°$, $-9 \leq h \leq 9$, $-12 \leq k \leq 12$, $-28 \leq l \leq 28$ yielding 3408 unique reflections (Rint = 0.0432). The intensity data were corrected for Lorentz and polarization effects and for absorption using SADABS[iii] (minimum and maximum transmission 0.6580, 0.7452).

The structure was solved by direct methods (SHELXS-97[iv]). Refinement was by full-matrix least squares based on F^2 using SHELXL-97.[v] All reflections were used during refinement. The weighting scheme used was $w=1/[\sigma^2(F_o^2) + (0.0828P)^2 + 1.3825P]$ where $P = (F_o^2 + 2F_c^2)/3$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using a riding model. Refinement converged to R1=0.0541 and wR2=0.1496 for 3085 observed reflections for which $F > 4\sigma(F)$ and R1=0.0601 and wR2=0.1540 and GOF =1.116 for all 3408 unique, non-zero reflections and 230 variables.[vi] The maximum Δ/σ in the final cycle of least squares was 0.000 and the two most prominent peaks in the final difference Fourier were +0.370 and -0.518 $e/Å^3$.

Table 1. lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Tables 2. and 3. Anisotropic thermal parameters are in Table 4. Tables 5. and 6. list bond distances and bond angles. Figure 1. is an ORTEP[vii] representation of the molecule with 30% probability thermal ellipsoids displayed.

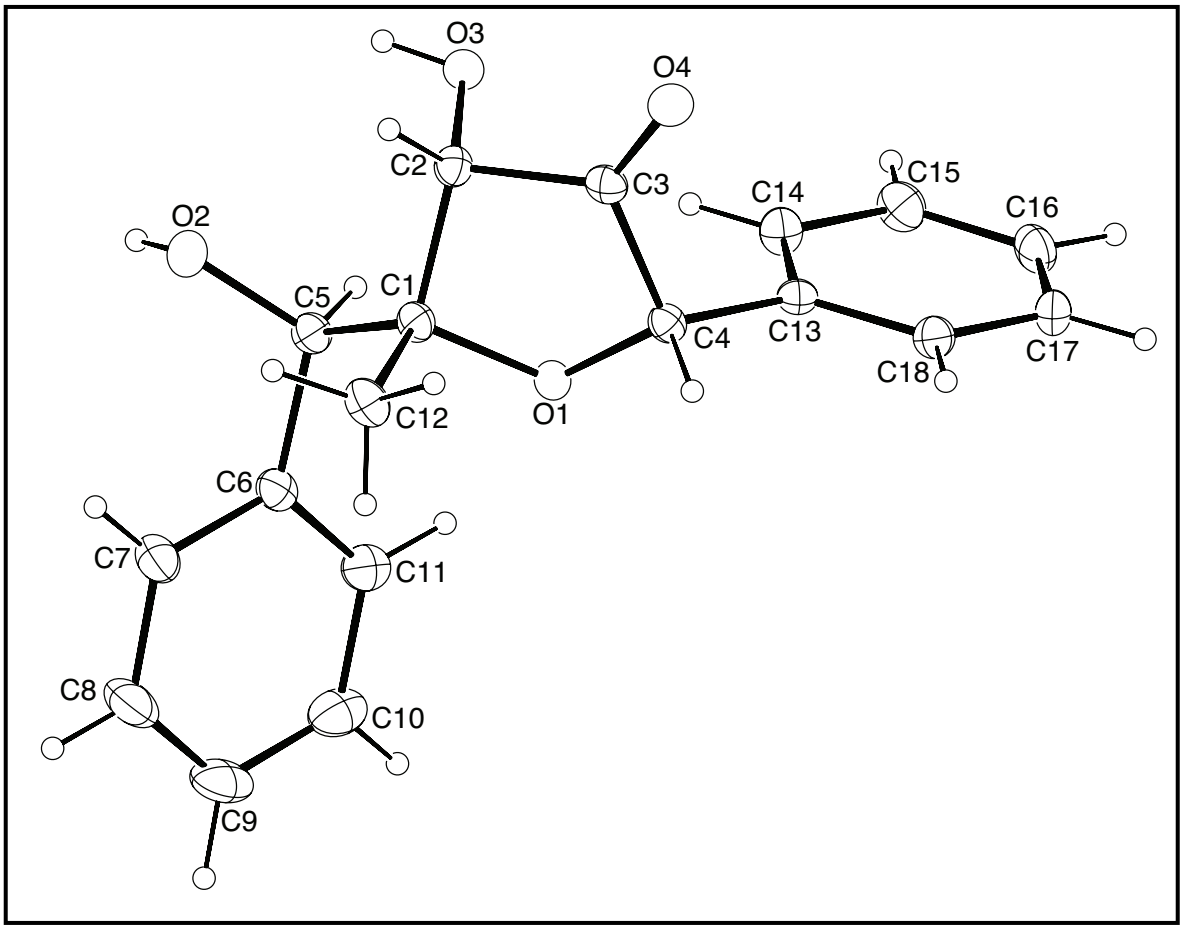


Figure 1. ORTEP drawing of the title compound with 30% probability thermal ellipsoids.

Table 1. Summary of Structure Determination of Compound 6181

Empirical formula	$C_{19}H_{20}O_4Cl_2$
Formula weight	383.25
Temperature	143(1) K
Wavelength	0.71073 Å
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Cell constants:	
a	7.8057(5) Å
b	10.1854(7) Å
c	23.4262(17) Å
Volume	1862.5(2) $Å^3$
Z	4
Density (calculated)	1.367 Mg/m^3
Absorption coefficient	0.369 mm^{-1}
F(000)	800
Crystal size	0.20 x 0.18 x 0.07 mm^3
Theta range for data collection	1.74 to 25.37°
Index ranges	$-9 \le h \le 9, -12 \le k \le 12, -28 \le l \le 28$
Reflections collected	31652
Independent reflections	3408 [R(int) = 0.0432]
Completeness to theta = 25.37°	99.7 %

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7452 and 0.6580
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3408 / 2 / 230
Goodness-of-fit on F^2	1.116
Final R indices [I>2sigma(I)]	R1 = 0.0541, wR2 = 0.1496
R indices (all data)	R1 = 0.0601, wR2 = 0.1540
Absolute structure parameter	0.64(14)
Largest diff. peak and hole	0.370 and -0.518 e.$Å^{-3}$

Table 2. Refined Positional Parameters for Compound 6181

Atom	x	y	z	U_{eq}, Å^2
C1	0.3462(4)	0.8590(3)	0.10339(12)	0.0238(6)
C2	0.4615(4)	0.8031(3)	0.05626(12)	0.0240(6)
C3	0.6017(4)	0.7393(3)	0.09140(12)	0.0234(6)
C4	0.5299(4)	0.7130(3)	0.15101(12)	0.0223(6)
C5	0.1578(4)	0.8633(3)	0.08750(12)	0.0251(6)
C6	0.0485(4)	0.9205(3)	0.13545(13)	0.0261(7)
C7	0.0110(5)	1.0543(3)	0.13719(15)	0.0373(8)
C8	-0.0795(5)	1.1069(4)	0.18253(17)	0.0486(10)
C9	-0.1371(5)	1.0269(4)	0.22633(16)	0.0483(10)
C10	-0.1038(5)	0.8942(4)	0.22411(15)	0.0429(9)
C11	-0.0108(4)	0.8407(4)	0.17908(13)	0.0332(7)
C12	0.4200(4)	0.9912(3)	0.12266(14)	0.0295(7)
C13	0.5281(4)	0.5690(3)	0.16593(12)	0.0236(6)
C14	0.4116(4)	0.4853(3)	0.13981(14)	0.0299(7)
C15	0.4108(5)	0.3527(3)	0.15360(15)	0.0343(8)
C16	0.5222(5)	0.3046(3)	0.19347(15)	0.0346(8)
C17	0.6396(5)	0.3861(3)	0.21937(13)	0.0335(7)
C18	0.6426(4)	0.5189(3)	0.20582(13)	0.0282(7)
O1	0.3601(3)	0.76251(19)	0.14918(8)	0.0230(4)
O2	0.1470(3)	0.9384(2)	0.03656(9)	0.0288(5)
O3	0.3867(3)	0.6999(2)	0.02421(9)	0.0287(5)
O4	0.7453(3)	0.7133(2)	0.07596(9)	0.0303(5)
C19	0.8011(6)	0.3520(6)	0.0545(2)	0.0834(18)
Cl1	0.9824(2)	0.42036(16)	0.08561(9)	0.1003(6)
Cl2	0.8522(3)	0.2297(2)	0.00505(8)	0.1031(6)

$U_{eq}=^{1}/_{3}[U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta+2U_{23}bb^*cc^*\cos\alpha]$

Table 3. Positional Parameters for Hydrogens in Compound 6181

Atom	x	y	z	U_{iso}, Å^2
H2	0.5068	0.8725	0.0315	0.032
H4	0.5966	0.7615	0.1795	0.030
H5	0.1187	0.7738	0.0795	0.033
H7	0.0472	1.1086	0.1076	0.050
H8	-0.1019	1.1965	0.1836	0.065
H9	-0.1976	1.0623	0.2569	0.064
H10	-0.1439	0.8397	0.2530	0.057
H11	0.0116	0.7511	0.1783	0.044
H12a	0.3661	1.0177	0.1577	0.044
H12b	0.3989	1.0562	0.0938	0.044
H12c	0.5412	0.9827	0.1286	0.044
H14	0.3342	0.5179	0.1132	0.040
H15	0.3342	0.2963	0.1356	0.046
H16	0.5188	0.2161	0.2032	0.046
H17	0.7167	0.3524	0.2459	0.045
H18	0.7211	0.5743	0.2234	0.038
H2a	0.0521	0.9286	0.0222	0.043
H3	0.3256	0.7309	-0.0009	0.043
H19a	0.7365	0.4206	0.0355	0.111
H19b	0.7290	0.3149	0.0841	0.111

Table 4. Refined Thermal Parameters (U's) for Compound 6181

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	0.0289(16)	0.0169(13)	0.0254(14)	-0.0001(11)	-0.0008(13)	-0.0006(12)
C2	0.0239(16)	0.0236(15)	0.0246(14)	0.0022(12)	0.0001(11)	0.0002(12)
C3	0.0267(16)	0.0174(14)	0.0261(14)	-0.0033(11)	0.0012(12)	-0.0035(12)
C4	0.0198(14)	0.0220(14)	0.0249(14)	-0.0015(12)	-0.0007(11)	0.0003(12)
C5	0.0296(16)	0.0191(13)	0.0266(15)	-0.0006(11)	-0.0002(13)	-0.0013(12)
C6	0.0205(15)	0.0285(15)	0.0293(15)	-0.0046(13)	-0.0041(12)	0.0019(12)
C7	0.036(2)	0.0356(18)	0.0402(19)	-0.0035(15)	-0.0017(16)	0.0106(16)
C8	0.044(2)	0.048(2)	0.053(2)	-0.0155(19)	0.0013(18)	0.0192(18)
C9	0.0282(19)	0.074(3)	0.043(2)	-0.019(2)	0.0042(16)	0.0120(19)
C10	0.0265(18)	0.068(3)	0.0338(18)	-0.0025(17)	0.0031(14)	-0.0011(17)
C11	0.0265(17)	0.0399(18)	0.0333(17)	-0.0026(14)	-0.0006(14)	-0.0013(14)
C12	0.0273(16)	0.0204(14)	0.0406(17)	-0.0037(13)	-0.0020(13)	-0.0038(13)
C13	0.0239(15)	0.0260(15)	0.0209(13)	-0.0002(12)	0.0043(11)	0.0020(12)
C14	0.0287(17)	0.0276(16)	0.0333(16)	0.0007(13)	-0.0034(13)	-0.0012(13)
C15	0.0365(19)	0.0261(16)	0.0404(18)	-0.0010(14)	0.0004(14)	-0.0036(14)
C16	0.042(2)	0.0227(15)	0.0395(18)	0.0061(14)	0.0076(15)	0.0056(15)
C17	0.0373(19)	0.0346(17)	0.0286(16)	0.0060(13)	-0.0007(14)	0.0136(15)
C18	0.0259(16)	0.0319(16)	0.0269(15)	-0.0004(12)	-0.0011(13)	0.0030(14)
O1	0.0238(10)	0.0217(10)	0.0236(10)	0.0018(8)	0.0010(8)	0.0022(8)
O2	0.0290(12)	0.0278(11)	0.0295(11)	0.0029(9)	-0.0036(9)	0.0002(10)
O3	0.0332(13)	0.0283(11)	0.0246(10)	-0.0039(9)	-0.0043(9)	0.0059(10)
O4	0.0271(12)	0.0364(12)	0.0275(11)	0.0005(10)	0.0028(9)	0.0017(10)
C19	0.063(3)	0.113(5)	0.074(3)	0.042(3)	0.014(3)	0.034(3)
Cl1	0.0719(10)	0.0773(10)	0.1518(16)	-0.0019(10)	-0.0034(10)	0.0175(8)
Cl2	0.0954(12)	0.1112(13)	0.1027(12)	0.0114(10)	-0.0278(10)	0.0173(10)

The form of the anisotropic displacement parameter is:
$\exp[-2\pi^2(a^{*2}U_{11}h^2+b^{*2}U_{22}k^2+c^{*2}U_{33}l^2+2b^*c^*U_{23}kl+2a^*c^*U_{13}hl+2a^*b^*U_{12}hk)]$

Table 5. Bond Distances in Compound 6181, Å

C1-O1	1.459(3)	C1-C5	1.518(4)	C1-C12	1.533(4)
C1-C2	1.534(4)	C2-O3	1.418(4)	C2-C3	1.516(4)
C3-O4	1.207(4)	C3-C4	1.528(4)	C4-O1	1.418(4)
C4-C13	1.508(4)	C5-O2	1.419(3)	C5-C6	1.526(4)
C6-C11	1.385(5)	C6-C7	1.395(5)	C7-C8	1.384(5)
C8-C9	1.385(6)	C9-C10	1.377(6)	C10-C11	1.391(5)
C13-C14	1.389(5)	C13-C18	1.390(4)	C14-C15	1.389(5)
C15-C16	1.367(5)	C16-C17	1.377(5)	C17-C18	1.390(5)
C19-Cl1	1.737(6)	C19-Cl2	1.747(6)		

Table 6. Bond Angles in Compound 6181, °

O1-C1-C5	105.8(2)	O1-C1-C12	110.3(2)	C5-C1-C12	114.3(2)
O1-C1-C2	103.6(2)	C5-C1-C2	113.8(2)	C12-C1-C2	108.5(3)
O3-C2-C3	105.5(2)	O3-C2-C1	114.5(2)	C3-C2-C1	101.1(2)
O4-C3-C2	127.0(3)	O4-C3-C4	125.2(3)	C2-C3-C4	107.9(2)
O1-C4-C13	110.1(2)	O1-C4-C3	104.6(2)	C13-C4-C3	112.7(2)
O2-C5-C1	106.2(2)	O2-C5-C6	112.4(2)	C1-C5-C6	111.9(2)
C11-C6-C7	118.8(3)	C11-C6-C5	120.4(3)	C7-C6-C5	120.7(3)
C8-C7-C6	120.5(4)	C7-C8-C9	120.5(4)	C10-C9-C8	119.2(3)
C9-C10-C11	120.8(4)	C6-C11-C10	120.3(3)	C14-C13-C18	119.5(3)
C14-C13-C4	120.1(3)	C18-C13-C4	120.4(3)	C13-C14-C15	119.8(3)
C16-C15-C14	120.3(3)	C15-C16-C17	120.6(3)	C16-C17-C18	119.8(3)

C17-C18-C13	120.0(3)	C4-O1-C1	109.4(2)	Cl1-C19-Cl2	112.2(3)

[i]Bruker (2009) SAINT. Bruker AXS Inc., Madison, Wisconsin, USA.

[ii]Bruker (2009) SHELXTL. Bruker AXS Inc., Madison, Wisconsin, USA.

[iii]Sheldrick, G.M. (2007) SADABS. University of Gottingen, Germany.

[iv]Sheldrick, G.M. (2008) Acta Cryst. A64,112-122.

[v]Sheldrick, G.M. (2008) Acta Cryst. A64,112-122.

[vi]$R1 = \Sigma||F_o| - |F_c|| / \Sigma |F_o|$

$wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{½}$

$GOF = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{½}$

where n = the number of reflections and p = the number of parameters refined.

[vii]"ORTEP-II: A Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustrations". C.K. Johnson (1976) ORNL-5138.